Tolbutamide-induced Improvement in Carbohydrate Tolerance of Young People with Mild Diabetes Mellitus

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Sulfonylurea drugs have been found to reduce fasting hyperglycemia of some young diabetic patients.[1,2] In such cases the diabetic state has been apparent for only a short period of time and resembles that seen in the adult or stable form of the disease. Our own studies,[3] as well as those of most other investigators,[4-7] have indicated that short-term administration of tolbutamide to the stable diabetic may correct fasting hyperglycemia but does not change significantly the height or duration of the hyperglycemic response to glucose (the so-called tolerance for glucose). However, systematic studies have not been reported to indicate whether more prolonged administration of sulfonylurea drugs may influence carbohydrate tolerance in such patients.

The present study was undertaken to investigate the effect of therapy with sulfonylurea drugs on carbohydrate tolerance of young, nonobese patients with mild, asymptomatic diabetes mellitus. The results indicate that in such subjects chronic administration of tolbutamide for two to twenty-two months not only may improve but may actually normalize tolerance for carbohydrate.

SUBJECTS AND METHODS

Fourteen nonobese subjects with asymptomatic diabetes were studied. Their ages ranged between eleven and thirty-five years (tables 1 and 2). In thirteen of the fourteen subjects the diagnosis became apparent for the first time when routine glucose tolerance tests were performed because of the existence of a strong family history of diabetes. The fasting blood sugar levels were below 100 mg. per cent in six subjects, between 100 and 120 mg. per cent in five, and between 130 and 210 mg. per cent in the remaining three subjects. Using a standard high carbohydrate preparatory diet and a true blood sugar method, glucose tolerance tests were considered diagnostic of the diabetic state when the blood sugar levels were or exceeded 160 mg./100 ml. at one hour, 140 mg./100 ml. at one and a half hours and 120 mg./100 ml. at two hours.[8] In the figures a diabetic curve is one in which all points lie at or above the upper border of the shaded triangle. In subjects with only mild but diagnostic diminution of glucose tolerance, tests for confirmation were repeated at least once before tolbutamide was given. Unless otherwise indicated, tolbutamide was given in a dosage of ½ gm. twice daily.* Diets used in conjunction with the drug contained 225 to 250 gm. of carbohydrate and maintenance calories. Glucose tolerance tests were repeated at intervals of two to four months, for as long as twenty-seven months, after the beginning of therapy. In the majority of instances tolbutamide was not given for one to four days preceding follow-up tests. Because of its short half life, tolbutamide blood levels are insignificant thirty-six hours after administration of the last dose.[9] On some occasions tolbutamide was given until the evening before the test. In cases in which glucose tolerance had returned to or near normal, cortisone-glucose tolerance tests were given.[8] An abnormal cortisone-glucose test is one in which all blood sugar levels are at or above 160 mg./100 ml. at one hour, 150 mg./100 ml. at one and a half hours, and 140 mg./100 ml. at two hours.

RESULTS

Table 1 summarizes the data of seven of the fourteen subjects. The pretreatment fasting blood sugar levels of this group of patients ranged between 79 and 113 mg./100 ml. Within two to four months of administration of tolbutamide (TBA) glucose tolerance became normal in this group of patients. Prior to the performance of each test, TBA had been withdrawn

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TABLE 1

Effect of tolbutamide (TBA) on glucose tolerance in patients with mild asymptomatic diabetes mellitus

Patient No.	Initials	Age, sex	FBS initial	FBS TBA	Glucose tolerance following TBA administration: Normal — Two days off TBA	Normal — On TBA	Improved — One to two days off	Improved — On TBA	Not improved	Remarks
1.	M.W.	25,M	113	74	+(3,16)		+(6,9,12)	+(10,12)		
2.	G.S.	31,M	102	97	+(4,9,18)					Diabetic GTT three months off TBA (9-12)
3.	Da. W.	21,M	97	77	+(3,6,9)		+(13,18)	+(10)		
4.	Ga. W.	18,F	93	80	+(2)					Normal GTT three, six and eight months off TBA
5.	L.S.	35,M	80	78	+(4,16)			+(24,27)		Diabetic GTT two and five months off TBA (16-21)
6.	E.M.	32,F	89	73	+(3,7)		+(11) one week off			
7.	P.C.	35,F	79	81	+(3,7)					Diabetes known for three years. On 10 units Lente previously (see text).

Figures in parentheses = months after first administration of TBA.

for at least two days. The cortisone-glucose tolerance test gave abnormal responses in five and a normal response in one (patient 2) of six patients tested (patients 1-6). In several patients one or more subsequent glucose tolerance tests again gave mildly abnormal results but carbohydrate tolerance was still greatly improved as compared to pretherapy tolerance.

The results obtained in patient 1 are shown in figure 1. After three months of TBA therapy glucose tolerance was normal. However, the cortisone-glucose tolerance test gave an abnormal response. After six, nine, ten and twelve months of TBA, glucose tolerance was mildly abnormal by our criteria but still greatly improved over pretherapy tolerance. The results of the test performed at ten months are shown in figure 1. The three-hour blood sugar level of 54 mg./100 ml. is to be noted.

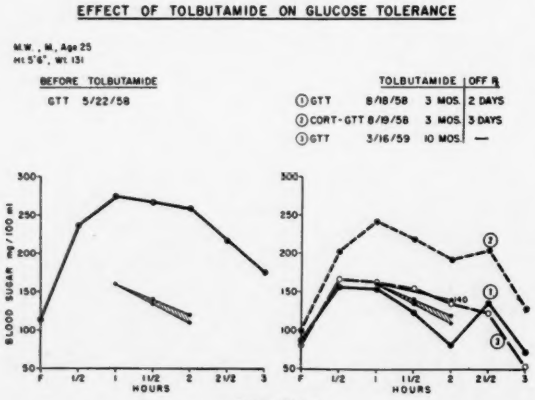
EFFECT OF TOLBUTAMIDE ON GLUCOSE TOLERANCE
M.W., M., Age 25
Ht. 5'6", Wt. 131
BEFORE TOLBUTAMIDE
GTT 5/22/58
TOLBUTAMIDE | OFF Rx
① GTT 8/18/58 3 MOS. 2 DAYS
② CORT-GTT 8/19/58 3 MOS. 3 DAYS
③ GTT 3/16/59 10 MOS. —
BLOOD SUGAR mg/100 ml
HOURS

FIGURE 1

After sixteen months of TBA therapy glucose tolerance was again normal.

In patient 2, G.S., glucose tolerance was normal after four and nine months of TBA therapy. TBA was then discontinued. Three months later glucose tolerance was abnormal again. Resumption of administration of TBA resulted in normal glucose tolerance when tested six months later.

Patient 4, Ga. W., age eighteen, was taken off TBA when glucose tolerance had become normal after two months of drug therapy. Three, six and eight months later glucose tolerance was still normal. The patient had been pregnant for two, five and seven months respectively at those times.

On the other hand, in patient 5, L.S., glucose tolerance became abnormal again after discontinuation of TBA therapy. Figure 2 illustrates these findings. Although glucose tolerance was only mildly abnormal, it did not improve after three or five months of a low carbohy-

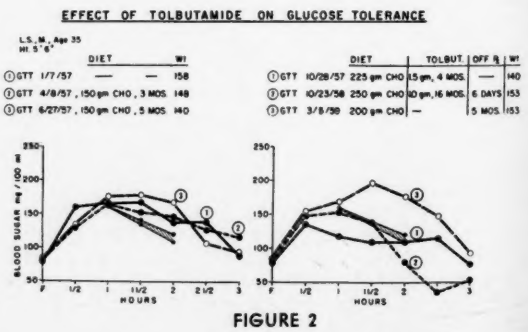
EFFECT OF TOLBUTAMIDE ON GLUCOSE TOLERANCE
L.S., M., Age 35
Ht. 5'6"
DIET | Wt
① GTT 1/7/57 — — 158
② GTT 4/8/57, 150 gm CHO, 3 MOS. 148
③ GTT 6/27/57, 150 gm CHO, 5 MOS. 140
DIET | TOLBUT. | OFF Rx | Wt
① GTT 10/28/57 225 gm CHO 15 gm, 4 MOS. — 140
② GTT 10/23/58 250 gm CHO 10 gm, 16 MOS. 6 DAYS 153
③ GTT 3/8/59 200 gm CHO — 5 MOS. 153
BLOOD SUGAR mg/100 ml
HOURS

FIGURE 2

drate, low calorie diet with a 10 or an 18 lb. weight loss. Tolbutamide therapy was then initiated. Four months later glucose tolerance was normal and remained normal for sixteen months in spite of a weight gain of 13 lb. The blood sugar levels of 37 mg./100 ml. at two and a half hours and 50 mg./100 ml. at three hours are to be noted (curve 2 on the right of figure 1). Tolbutamide was discontinued thereafter. Five months later glucose tolerance was abnormal again even though intake of carbohydrate had been curtailed and weight had been maintained (curve 3). Reinstitution of TBA therapy was again followed by improvement in glucose tolerance (table 1).

In patient 7, P.C., a thirty-five-year-old dietitian, the diagnosis of diabetes was made in April 1956. For several years before this diagnosis was made, the patient had had a voluntary dietary intake of 150 gm. of carbohydrate and 1800 calories. This diet was continued but the patient was advised to take 10 units of Lente insulin daily. Glucose tolerance tests were repeated, after the patient had been off insulin for ten days each time, in August 1956, August 1957 and February 1959. The first two glucose tolerance tests after initiation of insulin therapy gave normal results but the one done in February 1959 was similar to the initial one obtained in April 1956. The patient was then started on TBA. Three and seven months later glucose tolerance was normal.

Glucose tolerance was improved after initiation of tolbutamide therapy in the next six subjects (patients 8-13, table 2). In four of these improvement could be demonstrated after the drug had been withheld from one to two days while in two subjects (W.W. and De. W.) improvement could be shown only when the last dose of the drug was given the evening before the test. It should be noted that in this group improvement in carbohydrate tolerance or normal carbohydrate tolerance resulted from more prolonged administration of TBA than was necessary in the first group.

In patient 8, Gr. W., little change in glucose tolerance occurred during the first four months of TBA therapy when the drug had been withdrawn for two days before the test. After six months of TBA admin-

TABLE 2

Effect of tolbutamide (TBA) on glucose tolerance in patients with mild asymptomatic diabetes mellitus

Patient No.	Initials	Age, sex	FBS initial	FBS TBA	Glucose tolerance following TBA administration: Normal — Two days off TBA	Normal — On TBA	Improved — One to two days off	Improved — On TBA	Unimproved	Remarks
8.	Gr. W.	16,F	102	81	+(13,16)		+(6,7,10)	+(10)	(2)	
9.	F.P.	32,M	98	93	+(10½,15)		+(3,7)		(7½) on TBA	Diabetes known for five years. On 10 units of PZI for four years—GTT still abnormal
10.	Ge. W.	29,M	147	53-96		+(10)	+(3,13*)	(13,18)* (14,19)	Two days off TBA (9)†	FBS 53 mg.% (7) FBS 54 mg.% (9)
11.	T.W.	27,M	210 261	76-101		+(7)‡	+(3,11,14,17)	+(11,14)		
12.	W.W.	17,M	106	99		+(6½)		+(3½)	On TBA (1 & 2½) Two days off TBA (6½)	
13.	De W.	11,M	109	68-81				+(10,16)	1-2 days off TBA (2,6,10, 13,16)	
14.	C.J.	33,M	138	76					On TBA (7,15)	Diabetes known for nine years

*on 0.75 gm. †on 0.5 gm. ‡High peak, normal two-hour B.S. level

Figures in parentheses = months after first administration of TBA

istration, however, there was definite improvement in glucose tolerance. At ten months glucose tolerance was nearly normal when tested fourteen and thirty-eight hours after the last dose of TBA. After thirteen and sixteen months of therapy glucose tolerance was normal when TBA had been withdrawn for two days.

The results obtained in patient 10, Ge. W., are shown in figure 3. After three months of drug therapy little improvement in carbohydrate tolerance could be demonstrated when TBA was withheld for one day. After seven months the fasting blood sugar level was 53 mg./100 ml. When two months later the drug (½ gm./day as a single dose in the morning) was withheld for two days, there was no improvement in the fasting blood sugar level or in glucose tolerance. After ten months, again on a dose of 1 gm. per day, glucose tolerance was normal (curve 5) when TBA was given until the evening before the test. The fasting blood sugar was 58 mg./100 ml. and the three-hour blood sugar level was 37 mg./100 ml. After thirteen months glucose tolerance was still greatly improved when .75 gm. was given daily until the evening before the test. One day without the drug (curve 7) resulted in a normal fasting blood sugar but in minor improvement in glucose tolerance. Nineteen months after initiation of therapy glucose tolerance was near normal, one gram having been given daily for one month until the evening before the test.

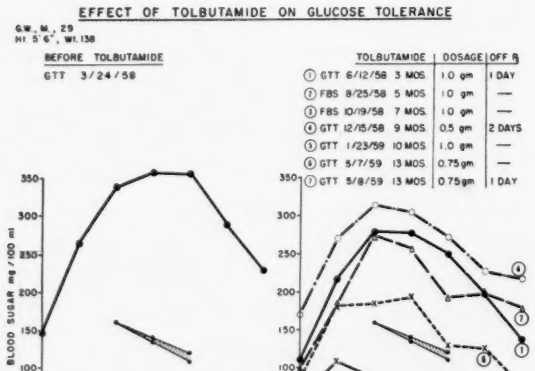
EFFECT OF TOLBUTAMIDE ON GLUCOSE TOLERANCE
G.W., M., 29
Ht. 5'6", Wt. 138
BEFORE TOLBUTAMIDE
GTT 3/24/58
TOLBUTAMIDE | DOSAGE | OFF
① GTT 6/12/58 3 MOS. 1.0 gm 1 DAY
② FBS 8/25/58 5 MOS. 1.0 gm —
③ FBS 10/19/58 7 MOS. 1.0 gm —
④ GTT 12/15/58 9 MOS. 0.5 gm 2 DAYS
⑤ GTT 1/23/59 10 MOS. 1.0 gm —
⑥ GTT 5/7/59 13 MOS. 0.75 gm —
⑦ GTT 5/8/59 13 MOS 0.75 gm 1 DAY
BLOOD SUGAR mg / 100 ml
HOURS

FIGURE 3

Patient 11, T.W., had fasting blood sugar levels of 210 and 261 mg./100 ml. initially (figure 4). The fasting blood sugar level decreased to normal after a few days of drug therapy but was elevated four months later when TBA was withdrawn for two days. After

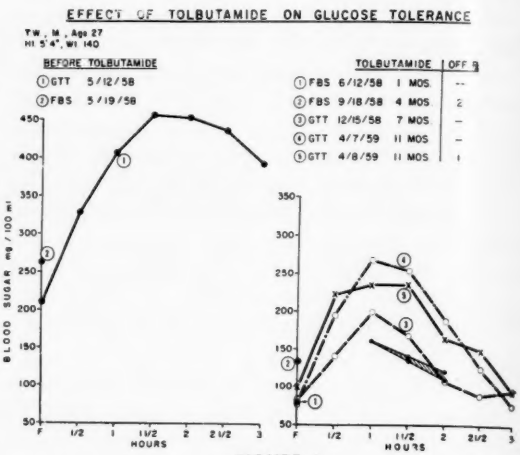
EFFECT OF TOLBUTAMIDE ON GLUCOSE TOLERANCE
T.W., M., Age 27
Ht. 5'4", Wt. 140
BEFORE TOLBUTAMIDE
① GTT 5/12/58
② FBS 5/19/58
TOLBUTAMIDE | OFF
① FBS 6/12/58 1 MOS. --
② FBS 9/18/58 4 MOS. 2
③ GTT 12/15/58 7 MOS. —
④ GTT 4/7/59 11 MOS. —
⑤ GTT 4/8/59 11 MOS. 1
BLOOD SUGAR mg / 100 ml
HOURS

FIGURE 4

seven months of TBA therapy (curve 3) the glucose tolerance test showed an elevated peak but a normal two-hour blood sugar level. The drug had been given until the evening before the test. After eleven months of therapy glucose tolerance was abnormal but nevertheless better than before treatment. There was no difference whether the drug was given until the evening before or had been omitted for one day before the test. Identical results were obtained after fourteen and seventeen months of TBA therapy.

In patient 12, W.W., age seventeen, there was no improvement in carbohydrate tolerance after one and two and a half months of TBA therapy but after three and a half months some improvement had occurred. After six and a half months glucose tolerance was normal when the drug was given until the evening before the test but unimproved when the drug was withheld for two days.

In patient 13, De. W., age eleven, improvement in glucose tolerance was apparent for the first time after ten months of therapy and then only when the drug was given until the evening before the test. Even after sixteen months there was no improvement in glucose tolerance when the drug had been stopped for one day before the test.

Patient 14, C.J., age thirty-three, showed no improvement in glucose tolerance during fifteen months of TBA therapy although the fasting blood sugar level became normal. This patient had been known to have diabetes for nine years.

DISCUSSION

These results indicate that over the short period of time covered by this study (up to twenty-seven months)

carbohydrate tolerance of young patients with mild asymptomatic diabetes may be greatly improved under the influence of tolbutamide. Although spontaneous improvement in carbohydrate tolerance occurs frequently in mild diabetics the tolbutamide results cannot be explained on this basis. In several of our patients diminished carbohydrate tolerance was stable or becoming more severe (patients 3, 4, 5, 7, and 13) before TBA therapy was begun. After TBA therapy, improvement in varying degrees occurred in all of the patients.

Since this investigation was undertaken as a pilot study, matched subjects with mild diabetes were not employed to evaluate the effect of diet therapy alone on glucose tolerance. However, information is available in many of these subjects to indicate that dietary changes by themselves were not responsible for improvement in glucose tolerance. In patient 2, glucose tolerance was normal after four and nine months of TBA therapy. Three months after discontinuance of TBA, but still on the same diet, glucose tolerance was abnormal again. In patient 4, initiation of a 225 gm. carbohydrate diet furnished approximately 40 gm. more of carbohydrate than her previous usual intake. In patient 5, the effect of TBA could be clearly disassociated from limitation of carbohydrate or calories as previously discussed. In patient 6, withdrawal of TBA for one week caused a reversion from normal to abnormal tolerance. Patient 7 had been on a 150 gm. carbohydrate, 1800 calorie diet for years before initiation of TBA. Patient 9 had been on a diet containing 225 gm. of carbohydrate and maintenance calories for four years before initiation of TBA therapy. In patients 10, 11, 12 and 13, discontinuance of TBA for one or two days caused loss of glucose tolerance so that diet alone could not have accounted for the great improvement demonstrated.

Normalization of the response to a glucose load, the occurrence of fasting hypoglycemia in one patient and the finding in some cases of postglucose hypoglycemia all suggest increased secretion of insulin as an important mode of action of tolbutamide in these patients. In addition, the finding of postglucose hypoglycemia suggests that the initial defect in the young as well as in the middle-aged diabetic is failure to release insulin quickly in response to hyperglycemia.[10]

In a considerable number of the patients tolbutamide was administered for more than three months and up to thirteen months before improved or normal carbohydrate tolerance could be demonstrated. More extensive studies and continued follow-up of the patients reported upon are needed to determine whether prolonged treatment with sulfonylureas can prevent decompensation of islet cell function in young mildly diabetic patients. Experience with the present group of patients suggests that if this goal is to be reached diabetes must be discovered and treated at a time when islet cell function can still be materially augmented.

Maclean and Oglivie[11] have shown that the size of the islets of Langerhans and the proportion and weight of islet tissue were greater in young patients with "acute" diabetes (death within eight weeks of onset of symptoms) than in "chronic" diabetes, and in the same range as in nondiabetic controls. Indeed, "acute" diabetes in the young may be accompanied by initial hyperplasia of the islets. However, with increasing duration of the disease there is a diminution of islet tissue to levels which are usually found in young "chronic" diabetics. It seems reasonable to assume that abnormality of islet cell function exists in spite of normal islet cell histology early in the course of the disease. Since all of our young diabetic patients were asymptomatic and were discovered before the onset of symptoms it can be assumed that there was preservation of normal islet cell tissue in most. With preservation of normal islet cell histology administration of tolbutamide may be able to improve islet cell function in young asymptomatic diabetics. Conceivably, tolbutamide may improve islet cell function by either stimulating the beta cells to increase the rate of insulin release and insulin production or by increasing the number of beta cells. However, in patient 14 in whom diabetes was known to have existed for nine years, administration of tolbutamide for as long as fifteen months was ineffective in improving glucose tolerance although the fasting blood sugar level fell to normal.

Little is known of the possible factors which induce initial abnormalities of carbohydrate tolerance in individuals genetically predisposed to diabetes mellitus. Increased secretion of growth hormone has been postulated to be one such possible factor in young patients.[12] It is of interest therefore that Mirsky has reported that administration of tolbutamide to dogs prevents or decreases the diabetogenic effect of administered growth hormone.[13] In addition, Owen has shown that tolbutamide is effective in lowering postprandial hyperglycemia in rats whose carbohydrate tolerance is impaired by growth hormone and a high carbohydrate diet.[14]

Several other references in the literature are of interest in connection with these studies. In 1956 Kinsell and his associates[15] reported that administration of carbutamide to a nine-year-old child who had had diabetic glucose tolerance tests over a period of one year caused progressive normalization of carbohydrate tolerance. This

patient developed fasting hypoglycemia while taking .5 gm. of carbutamide daily.

Heineman and his associates[16] found improvement in intravenous glucose tolerance of one patient after prolonged therapy with carbutamide. Lundbaek and his associates[17] demonstrated mild improvement in oral and intravenous glucose tolerance during the administration of carbutamide, tolbutamide and chlorpropamide. Although the last two groups of investigators did not indicate the ages of their patients, these were presumably the usual middle-aged, sulfonylurea-responsive diabetic patients.

SUMMARY

1. Carbohydrate tolerance improved or became normal in thirteen of fourteen young, nonobese, mild diabetic patients during treatment with tolbutamide over a period of two to twenty-two months.

2. Normalization of the response to a glucose load as well as occurrence of fasting and postprandial hypoglycemia suggest increased insulin secretion as a mode of action of tolbutamide in these patients.

3. The studies reported could have important bearing on the problem of prevention of diabetes mellitus.

SUMMARIO IN INTERLINGUA

Melioration, Effectuate per Tolbutamida, in le Tolerantia pro Hydrato de Carbon in Patientes de Juvene Etates con Leve Grados de Diabete Mellite

1. Le tolerantia pro hydrato de carbon se meliorava o deveniva normal in dece-tres ex dece-quatro non-obese patientes de juvene etates con leve grados de diabete durante periodos de duo a vinti-duo menses de tractamento con tolbutamida.

2. Le normalisation del responsa a cargas de glucosa e etiam le occurrentia de hypoglycemia in stato jejun e post prandios pare reflecter un augmento del secretion de insulina como modo de action del tolbutamida in iste patientes.

3. Le studios hic reportate es possibilemente de alte importantia pro le problema del prevention de diabete mellite.

ACKNOWLEDGMENT

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The Effect of Blood Glucose Concentration on Insulin Output

Robert Metz, M.B., Chicago

The available evidence concerning the effect of the blood sugar level on the output of insulin from the pancreas permits only the limited conclusion that extra insulin is liberated in the presence of hyperglycemia.[1,2] There is no evidence to support a more precise delineation of this relationship.

The purpose of the present study was to explore the quantitative aspects of the effect of blood glucose concentrations, both high and low, on the rate of insulin secretion in the dog. The insulin-like activity of blood drawn from the pancreatic vein was determined by bioassay, using the isolated rat-diaphragm technic. Hypoglycemia was produced by pretreatment with phloridzin, and hyperglycemia was produced by intravenous glucose infusion.

The results of this experiment indicate that the rate of insulin secretion is a continuous function of the blood sugar concentration. Information has been obtained about the form of this relationship, as well as the actual quantities of insulin secreted in the presence of normoglycemia, hypoglycemia and hyperglycemia.

MATERIALS AND METHODS

Seven male dogs were used. Four of them were given 10 ml. of a 20 per cent solution of phloridzin in propylene glycol, administered subcutaneously twice daily on the two days preceding the experiment. All animals were fasted for eighteen hours before the experiment. They were anesthetized with intravenous sodium pentobarbital. The abdomen was entered and the pancreaticoduodenal vein exposed. A plastic cannula, having about the same diameter as the vein, was introduced in a retrograde direction and secured with its tip lying just within the margin of the pancreas. The dog was heparinized, and the pancreatic venous effluent was allowed to drain continuously into graduated tubes; by timing the inflow into these tubes a measure of the flow rate was obtained. Aliquots of the effluent were collected before, and at intervals after, the start of an infusion of dextrose in water into a femoral vein. The infusion rate was varied from time to time to produce differing rates of increment of the blood glucose levels. The aliquots were collected under oil into the graduated tubes, and the plasma was separated by centrifugation and stored at 4° C. pending the performance of the assays.

The technic used for the assays was essentially that first successfully used by Groen and his associates,[3] and described more recently by Wright.[4] Male Sprague-Dawley rats weighing between 100 and 200 gm. were used. In any one run the weights of the rats did not vary by more than 10 gm. The rats were fasted for eighteen to twenty-four hours and killed by decapitation. The diaphragms were carefully removed and bisected, and each pair of hemidiaphragms was soaked in a Glucose-Krebs-Ringer-Bicarbonate (G.K.R.B.) solution at 4° C. for fifteen minutes. After soaking, hemidiaphragms were transferred to separate 10 ml. Erlenmeyer flasks for incubation. This was done on a Dubnoff incubator for one hour at 37° C. under an atmosphere of 95 per cent O_2 and 5 per cent CO_2. For incubation 1 ml. of either plasma (unknowns), G.K.R.B. (controls) or G.K.R.B. containing known concentrations of insulin (standards), adjusted to equal glucose concentrations, was used. At the end of the incubation period the hemidiaphragms were removed and placed in an oven at 110° C. overnight and weighed the next day. The glucose concentration of the medium, which had been measured before incubation, was remeasured, and the quantity of glucose consumed by the hemidiaphragm during incubation was calculated. The glucose uptake was expressed as milligrams of glucose per gram dry weight of diaphragm per sixty minutes. Each sample was assayed in duplicate. In each run the mean uptake of the diaphragms incubated in the control (G.K.R.B.) was subtracted from the mean uptakes of the diaphragms incubated in the respective unknowns or standards, to give the increment in glucose uptake produced by the insulin in the medium. The insulin concentration of

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each plasma sample was read from a calibration curve prepared by plotting increments in glucose uptake as a function of known insulin concentration, and expressed as milli-units (mU.) of insulin per 100 ml. of plasma.

RESULTS

Standardization and estimation of the reliability of the assay: From time to time during the course of this investigation, assay runs were performed on standard solutions of insulin in G.K.R.B. The results from all these determinations were pooled (table 1) to construct the calibration curve. The results indicated an apparently linear log-dose-response curve, as reported by other investigators. The slope of the curve, 0.6, was in close agreement with the range of slopes reported by Randle.[5]

Several samples of arterial blood, obtained from anesthetized dogs, were assayed. The mean insulin concentration of thirteen samples was 16 mU. per 100 ml., a value similar to those reported for both human and dog venous blood by others.[3,4] As a further check of the assay, insulin was added to samples of pooled peripheral blood plasma to produce insulin concentrations in the range encountered in pancreatic venous plasma, and the insulin enriched plasma was then assayed. Duplicate assays were run on ten samples to which 0, 100, 500 and 1,000 mU. per 100 ml. were added, respectively. That the method was not subject to gross systematic error is indicated by the small systematic deviation of the points from the line (figure 1), which theoretically would represent perfect recovery.

TABLE 1

Increment in glucose uptake produced by various concentrations of insulin in G.K.R.B. (mean values)

Insulin concentration (mU./100 ml.)	No. of determinations	Increment in glucose uptake	S.E.
10	9	2.5	.69
100	14	10.5	.62
500	5	15.3	.84
1,000	13	19.4	.50

To assess whether the random error of the assay method could have accounted for the observed differences in insulin concentration in the pancreatic venous blood samples, the deviation of paired results from their respective means was examined. An analysis of variance performed on the data indicated that the differences between paired observations were significantly different ($p<.01$) from the differences within pairs.

Measurement of insulin output: Twenty-five samples of pancreatic venous blood were obtained from seven

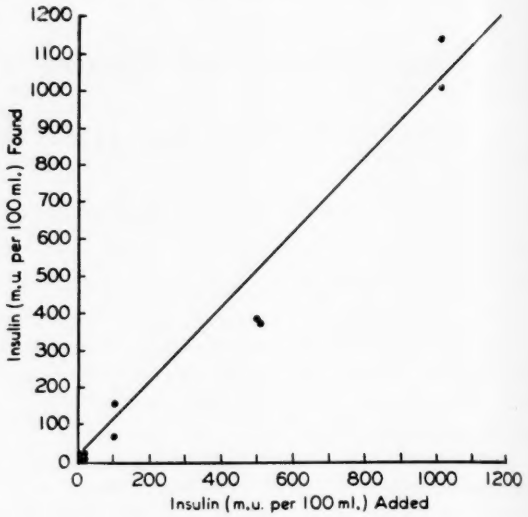

FIGURE 1

dogs. The blood glucose concentrations at the time of collection of the various samples ranged from 37 to 655 mg./100 ml. In the four phloridzinized dogs the blood sugars at the time of collection of the first pancreatic venous samples, that is, before the start of the glucose infusions, were between 37 and 72 mg./100 ml. The corresponding values for the other dogs were between 86 and 151 mg./100 ml. The flow rates from the cannula varied from 3.5 to 8 ml./min. In some of the animals there was an increase in flow rate as the experiment progressed; in others there was no change. Whereas plasma, and not whole blood insulin was measured, the figures for blood flow were multiplied by 6/10 in order to convert blood flow values to plasma flow. The insulin content of each sample, as determined by the bio-assay, was multiplied by the calculated plasma flow, the resultant being insulin output in mU./min. (table 2).

The results revealed a very wide range of insulin outputs, from 0.2 to 40 mU./min. It is apparent from table 2 that the insulin outputs increased as the blood sugar rose during the experiments. The data do not allow of a reliable estimation of the form of the relationship in each animal individually. But when the data from all the animals are simply combined, and plotted as log insulin output against log blood sugar, the result is apparently linear. Figure 2 presents this plot of the experimental points and the fitted regression equation, $\log Y = -3.14 + 1.64 \log X$. Figure 3 presents the original data and the corresponding exponential equation, $Y = 0.0007\ (X^{1.64})$. Obviously

TABLE 2

Blood glucose, pancreatic venous insulin concentration and blood flow, and calculated insulin output

Dog number	Pancreatic venous blood sample number	Peripheral venous blood glucose conc. (mg./100 ml.)	Insulin concentration (mU./100 ml.)	Flow rate (ml./min.)	Insulin output* (mU./min.)
1	1	37	10	3.5	0.2
	2	40	25	3.5	0.5
	3	389	425	4.5	11.5
	4	539	830	4.5	22.5
	5	528	500	4.5	13.5
2	6	151	52	3.5	1.1
	7	340	780	5.0	23.4
	8	422	505	7.0	21.2
	9	574	560	7.0	23.5
3	10	86	31	3.5	0.6
	11	306	570	3.5	12.0
	12	514	720	5.0	21.6
4	13	65	16	7.0	0.7
	14	426	135	7.0	5.7
	15	655	970	7.0	40.7
	16	577	380	7.0	16.0
5	17	42	28	3.5	0.6
	18	391	730	8.0	35.0
	19	658	790	8.0	37.9
6	20	127	90	5.0	2.7
	21	116	58	5.0	1.7
	22	236	130	5.0	3.9
	23	296	330	5.0	9.9
	24	246	205	5.0	6.2
7	25	72	26	4.5	0.7

*Insulin output = insulin concentration x 6/10 (blood flow rate).

this strictly empirical equation will not bear extrapolation, for at still higher glucose concentrations the insulin output would presumably level off at some maximum.

In view of the fact that the blood sugar levels were generally changing throughout these experiments, the results do not establish that the response of the pancreas is exclusively an instantaneous one to the concentration of glucose in the blood. There may be a lag in the response, or the response may be modified by the rate of change of glucose concentration. Although the data are not adequate to rule out these possibilities, it seems likely that if the level of insulin liberation is in fact modified by the rate of blood sugar change, the deviation of each of the individual points from the regression line might have been due in part, at least, to the rate of change at the time of collection of each of the samples.

Investigation of this point showed no significant correlation ($r = 0.17$) between deviation and the rate of change, suggesting that this factor had not influenced the pancreatic response.

DISCUSSION

The problem of the relationship of insulin output to the blood sugar level has been under investigation for more than thirty years (see Houssay[1] and Pozza[2] for a review of the literature on this subject). Previous studies have dealt almost exclusively with the effect of hyperglycemia, and the methods that have been used have not provided quantitative information. Ricketts[6] pointed out twenty years ago that the elucidation of the phenomena of insulin secretion would have to await a method for the measurement of the amount of insulin in the blood stream. The results reported in this study have been obtained by means of such a method. The reliability of these results depends, of course, on the reliability of the insulin assay method used.

The question of the specificity of this type of insulin assay procedure has not been completely settled, and doubt has been expressed concerning the nature of the "insulin-like activity" in blood.[7,8] In the present study, the finding of very much higher levels of "insulin-like activity" in the pancreatic venous blood as compared

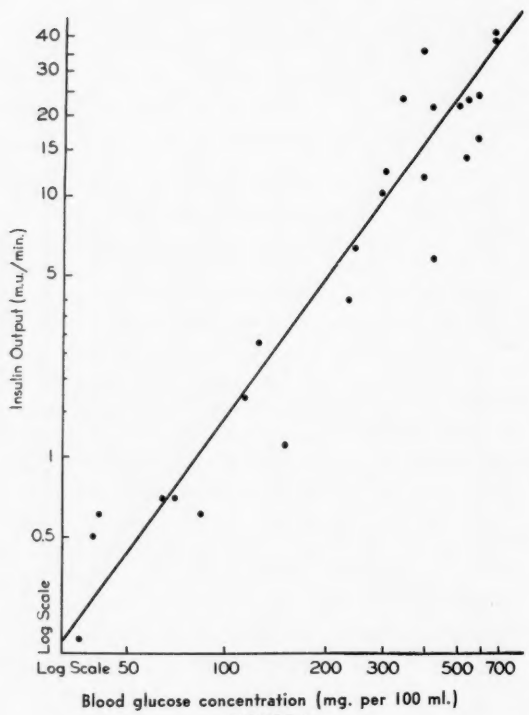

FIGURE 2

to peripheral blood, strongly supports the conclusions of those workers who have claimed that such activity is due to insulin itself.[3,6] Although a precise estimate of the systematic error of the assay was not made, there is reason to believe that the units used in this report do, in fact, correspond closely with the standard units used in the quantitation of insulin. The few assays that were performed on insulin enriched plasma showed almost quantitative recovery of the added insulin. Moreover, a rough calculation* of the daily insulin secretion in the dog, based on the figures obtained in this study, lends further support to the reliability of the figures.

The results obtained in this experiment clearly confirm the belief that hyperglycemia provokes the liberation of extra insulin from the pancreas. They show further that insulin output is a continuous positive function of the concentration of glucose in the blood, and that the response of the pancreas to changes in the blood glucose concentration probably is prompt, as even with a rapidly rising blood sugar, there was no evidence of a modification of the relationship between insulin output and the level of glycemia. It is apparent that this effect of blood sugar on insulin output may function as a negative feedback loop in the homeostatic regulation of blood sugar.

The lowest blood sugar recorded in the experiments was 37 mg./100 ml. and the corresponding insulin output was 0.2 mU./min. However, the 0.2 mU./min. flowing from the pancreatic vein may have represented merely circulating insulin, and there may have been no actual output at the time. At a blood sugar of 660 mg./100 ml. the output was about 40 mU./min. Thus the part of the pancreas drained by the pancreaticoduodenal vein was apparently able to respond to hyperglycemia by increasing insulin secretion from approximately zero to a level of about 2.5 units per hour.

The substantial decrease, or even cessation, of insulin output in the presence of low blood sugar values could have important consequences because of the differences in insulin responsiveness among the various tissues of the body. The shutting-off of the insulin supply in hypoglycemia would have the effect of decreasing glucose transport into insulin-sensitive tissues, such as muscle and adipose tissue, but would not, presumably, affect transport into brain cells with their insulin-independent glucose transport system. The brain would, therefore, be expected to receive a greater proportion of the available circulating glucose in time of glucose deficiency and less vital tissue a lesser proportion.

Some of the findings in this study may have a bearing on certain aspects of diabetes in the human being. The normal dog pancreas showed an enormous capacity to increase rapidly the supply of insulin to the body. If the human pancreas is similarly constituted, it seems not unlikely that the prediabetic and "mild" diabetic states could be an expression of an impairment of this capacity. This speculation receives support from the fact that appreciable and even, in some cases, normal quantities of insulin may be extracted from the pancreases of maturity onset diabetics.[9] Yet the distinguishing feature of this condition is an impaired ability to handle a glucose load, possibly due to an inadequate response on the part of the secretory mechanism of the pancreas.

It is seen that the effect of the blood sugar on the level of insulin liberation may be expressed graphically by a curved line with the concavity upward (figure 3). This suggests that insulin output might be a power

*Insulin output from the pancreatic vein in the presence of a blood sugar of 80 mg./100 ml. was about 1 mU/min. (figures 2 and 3). The pancreatic vein drains about one third of the pancreas, and that part of the organ where there is a lesser concentration of islets than in the tail. Therefore, insulin output from the whole organ would be, say, 4 mU/min., or approximately 6 units/24 hours. This figure must be close to the twenty-four-hour insulin requirement of a fasted dog.

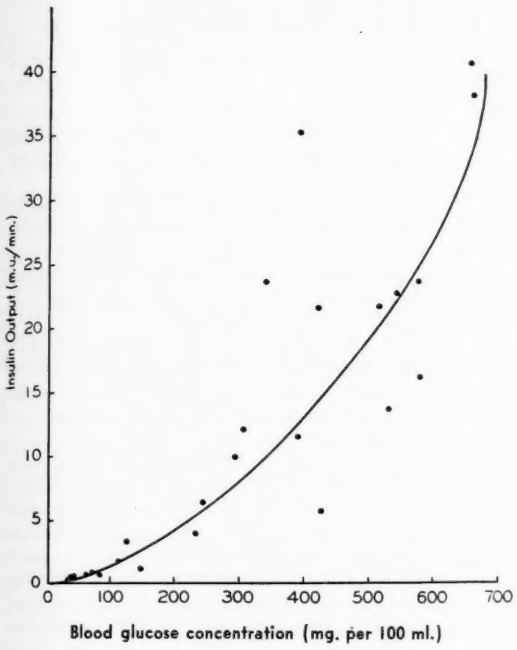

FIGURE 3

function of the glucose concentration, in which case a rise in blood sugar would result in a disproportionate increase in the demand on the pancreas, and the higher the blood sugar, the more potent would be the stimulatory effect. It may be seen (figures 2 and 3) that with a rise in blood sugar from 70 to 300 mg./100 ml., insulin output would be expected to increase from about 0.7 mU./min. to over 7 mU./min., that is, a fourfold increase in the glucose concentration at this level might result in a tenfold increase in the quantity of insulin liberated. If this "forced draught" effect of hyperglycemia exists in the human being, hyperglycemia, even if sporadic, could well hasten the exhaustion of an already compromised pancreas, such as probably exists in prediabetics and those diabetics with residual β-cell function.

SUMMARY

In acute experiments on anesthetized dogs, the venous effluent from a major part of the pancreas was continuously collected, its rate of flow recorded and its insulin concentration measured by the rat diaphragm technic. The rate of insulin secretion was thereby determined in response to lowering the blood sugar by pretreatment with phloridzin, and to elevating the blood sugar by continuous infusion of glucose intravenously. The rate of insulin secretion was found to be a continuous function of the blood sugar level, falling as low as 0.2 mU./min. in hypoglycemia (30-40 mg./100 ml.) and rising as high as 40 mU./min. in severe hyperglycemia (600-700 mg./100 ml.). This response of the pancreas to blood sugar concentration may well serve as a negative feedback loop in the regulation of the blood sugar level.

SUMMARIO IN INTERLINGUA

Le Effecto del Concentrationes de Glucosa Sanguinee Super le Rendimento de Insulina

In experimentos acute con canes anesthesiate, le effluxo venose ab un parte major del pancreas esseva colligite continuemente, le intensitate de su production esseva mesurate, e su concentration de insulina esseva estimate per le technica a diaphragma de ratto. Esseva determinate assi le responsa del secretion de insulina al reduction del sucro de sanguine effectuate per un pretractamento con phlorizina e al elevation del sucro de sanguine effectuate per un continue infusion intravenose de glucosa. Esseva constatate que le intensitate del secretion de insulina esseva un function continue del nivello del sucro de sanguine, descendente usque a 0,2 mU/min in hypoglycemia (30 a 40 mg per 100 ml) e montante usque a 40 mU/min in hyperglycemia sever (600 a 700 mg per 100 ml). Il es ben possibile que iste responsa del pancreas al concentration del sucro de sanguine age como un negative circuito de retro-effecto in le controlo del nivello de sucro in le sanguine.

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Gastric Hemorrhage in Diabetic Coma

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During severe diabetic acidosis or coma, gastric dilatation and retention of large quantities of food, gastric juice, and changed blood may occur and dark gastric content may be aspirated into the lungs after vomiting. At autopsy usually no single bleeding point is found[1] and the bleeding rarely is so severe that it threatens life. However, in the following case observed at the New England Deaconess Hospital, massive gastrointestinal hemorrhage occurred during and shortly after severe acidosis so that a subtotal gastrectomy became necessary to control the blood loss.

CASE REPORT

J.R., Case 22698, a white male aged thirty-one years, with diabetes mellitus for sixteen years, was admitted to the hospital in diabetic acidosis on July 28, 1958. His cooperation in following a strict diabetic diet or testing the glucose excretion in his urine had been poor. At the time of his annual or semiannual visits to the Joslin Clinic, blood sugar values varied between 210 and 540 mg. per 100 ml.

During the two months prior to this admission, the patient had noticed marked and progressive fatigue with headaches during the last week; nausea, vomiting and increasing drowsiness had been present for two days. On the day of admission, he was found unresponsive at home and after administration of 80 units of Regular Insulin he was admitted to the hospital as an emergency patient.

Physical examination revealed a normally developed, unconscious man with Kussmaul respiration. The skin was warm and dry. The temperature was 96° F. orally; the blood pressure 72 systolic, 10 diastolic; and the pulse 130 per minute. The pupils were dilated but reacted to light. The eyeballs were soft. A slight inflammation of the pharynx was present and the tongue was dry and coated. Heart and lungs were normal. The abdomen was scaphoid; diffuse muscle spasm of the abdominal wall made palpation of the intra-abdominal organs difficult but the liver seemed normal in size. No tympany was found and peristalsis was diminished. The deep tendon reflexes were hypoactive and the Babinski sign was absent bilaterally.

Laboratory findings: The true blood glucose on admission was 1,775 mg. per 100 ml., the plasma acetone was positive in a dilution of 1:8, and the plasma CO_2 was 10 mM per liter. The urine contained 20 mg. albumin per 100 ml., 4 gm. glucose per 100 ml., and 3+ acetone; the sediment contained no abnormal cells or casts. The hemoglobin was 11.1 gm. per 100 ml.; the white blood count 38,000 per cu. mm. with an increase in polymorphonuclear cells. The nonprotein nitrogen was 128 mg. per 100 ml., the chloride 68, the sodium 117, and the potassium 6.8 mEq. per liter.

Treatment was begun immediately with administration of 500 units of crystalline insulin. The stomach was evacuated and 1,700 cc. of dark brown material, which gave a positive reaction to guaiac, was obtained. A stool specimen was guaiac negative.

During the first eighteen hours in the hospital, a total of 1,000 units of crystalline insulin and 4,000 ml. of normal saline with 40 mEq. of sodium lactate and 20 mEq. of potassium chloride was given. At the end of this period the blood sugar value was 84 mg. per 100 ml. The patient was still obtunded but cooperative. Nausea persisted.

During the following day the stomach was emptied again of material still containing large amounts of blood. A stool specimen was now 4+ positive for guaiac. Because of increasing anemia, 250 ml. of packed red blood cells and 500 ml. of whole blood were transfused.

Recovery was slow during the following week. The appetite remained poor and small amounts of guaiac-positive material were vomited several times. The patient was placed on intermittent drainage[2] to relieve gastric distention and to measure the amount of gastric retention. Although persistent gastric residuum was present, definite obstruction of the upper gastrointestinal tract could not be demonstrated on X-ray examination. The esophagus was normal and no signs of an ulcer were found in the esophagus, stomach or duodenum. Bowel movements were tarry, loose, and guaiac positive for several days. During this period of time the potassium loss required replacement with 20-40 mEq. intravenously daily. Intercurrent bronchopneumonia with a temperature of 101° F. developed and was accompanied by a Monilia infection of the upper respiratory tract and cystitis. After treatment with antibiotics and sulfonamides, the fever gradually subsided.

The third hospital week began with an acute episode of massive gastrointestinal hemorrhage, which failed to respond to conservative medical therapy. At that time platelet count, bleeding time, and clotting time were normal. The prothrombin activity was 9 per cent of control but rose to 78 per cent after vitamin K injections. Despite this, bleeding continued and 14 units of whole blood (500 cc. each) were required in a period of seventy-two hours to maintain a hematocrit of 35 ml. per 100 ml.

Because of the suspicion of a duodenal ulcer on a second radiologic examination, a subtotal gastrectomy was performed on the seventeenth day after admission.

The postoperative course was uneventful with no further evidence of bleeding, and the patient was discharged ten days after the operation.

Examination of the resected stomach and the duodenal bulb failed to reveal a single bleeding point. On gross inspection coarseness and hyperemia of the mucosal folds were noted; microscopic examination showed dilated mucosal capillaries.

A specimen of the liver obtained during the operation revealed normal content of fat and glycogen.

The experience with this personally observed case was extended by analyzing the records of thirty patients who had been admitted to the New England Deaconess Hos-

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pital and did not survive severe diabetic acidosis or coma. Autopsy reports were available in all thirty cases and an attempt was made to correlate postmortem findings concerning abnormalities of the gastrointestinal tract and the liver with the clinical information obtained from their hospital records.

In eleven of these thirty cases gastrointestinal hemorrhage was observed clinically; grossly bloody material was either vomited or obtained by routine gastric lavage. At autopsy, erosions of the epithelial layers of the esophageal and gastric mucosa were found in one case; in three cases congestion of the gastric mucosa or capillary hemorrhage was noted; and in seven cases no pathologic changes were observed. In one other patient tarry, strongly guaiac-positive stools were explained by postmortem demonstration of multiple ulcerations in all parts of the gastrointestinal tract. Congestion, erosions, or ulcers in the stomach or duodenum were found in six cases in which no hemorrhage was mentioned in the clinical record.

DISCUSSION

At the present time the exact mechanism of hemorrhage into the gastrointestinal tract is not known but several theories have been developed.

Although liver damage with resulting hypoprothrombinemia and/or hypofibrinogenemia could theoretically contribute to the tendency for gastrointestinal hemorrhage during diabetic acidosis and coma, examination of the liver tissue in the cases studied at postmortem showed only varying degrees of fat and glycogen deposition. The latter may be explained in part by vigorous treatment with insulin prior to death.

According to Bradley, Sagild and Schertenleib,[5] in the absence of acute illness or unrelated liver disease, the incidence of abnormal liver function tests in 118 diabetic patients was 14.4 per cent. In a similar series, Frankel, Asbury and Baker reported an incidence of 12.9 per cent.[6] These statistics differ from those of Lewy, Ryan and Fineberg, who obtained at least two abnormal liver tests in 30.4 per cent of diabetic patients.[7]

As summarized by E. P. Joslin and co-workers[8] in reports of several hospitals, the incidence of hepatic cirrhosis at autopsy of diabetic patients usually was higher than in control series of nondiabetic patients.

TABLE 1

Clinical and postmortem examination in thirty cases of diabetic acidosis with respect to gastric hemorrhage

Clinical features		Findings at autopsy	
Evidence of hemorrhage in gastric contents	Liver enlarged	Gastrointestinal	Liver*
1. bloody vomitus	0	esophageal ulcer	fat+, glycogen+
2. " "	0	capillary hemorrhages	glycogen+
3. " "	0	mucosal hemorrhage	congestion
		congestion, thickening of intimal capillaries	
4. " "	0	congestion	normal
5. lavage	0	none	"
6. "	+	"	congestion
7. "	+	"	glycogen+
8. bloody vomitus	+	"	fat++
9. " "	0	"	fat+, glycogen++
10. lavage	0	"	fat++, glycogen++
11. tarry stools	0	ulcerations in esophagus, stomach, large and small intestine	fat+
12. no comment	0	duodenal ulcer	fat++, congestion
13. "	0	ecchymosis, petechiae	fat+, glyc.+, cong.
14. "	+	congestion	glycogen+, cong.
15. "	+	1 mm. ulcerations in stomach and esophagus	fat+, glycogen+ congestion
16. "	0	congestion	fat+, glycogen+
17. "	0	erosions, inflammation	focal necrosis
18. "	+	none	fat+
19. "	0	"	glycogen+
20. none	+	"	fat++, glycogen++
21. no comment	+	"	fat+
22. none	0	"	glycogen+
23. "	0	"	fat+, glycogen+
24. no comment	0	"	fat+, glycogen+
25. "	0	"	fat+, glycogen+
26. none	0	"	fat+, glycogen+
27. no comment	0	"	fat+, glycogen++
28. "	0	"	glycogen+
29. "	0	"	normal
30. "	0	"	"

*Concentrations of fat and glycogen described as normal, slightly increased +, or markedly increased ++.

An exact answer to the question, whether liver damage should be regarded as a factor contributing to gastrointestinal hemorrhage during diabetic acidosis or coma, cannot be given at the present time and requires more clinical information, such as determination of prothrombin activity and serum fibrinogen content in the blood during the acute phase of the disorder.

Congestive heart failure and shock may occur, especially in older patients during diabetic acidosis and coma, resulting in passive congestion of the abdominal viscera.

Such a state in the presence of other precipitating factors as capillary fragility and mechanical trauma may lead to gastrointestinal hemorrhage. At autopsy, dilatation of the right heart and congestion of internal organs were observed frequently in this series.

A mechanical factor probably is of major importance in precipitating intragastric bleeding under these conditions by reason of marked dilatation of the stomach. The latter may be so pronounced that the stomach occupies most of the abdominal cavity, as demonstrated by radiologic examinations.[9] With correction of the acidosis the stomach regains its normal tone. Capillary fragility is well documented in diabetic patients and may be accelerated by the metabolic derangement accompanying diabetic acidosis or coma. This factor, in the presence of venous stasis, may form the basis for hemorrhage into the dilated stomach.

According to Bernig,[10] gastric dilatation is caused by central paralysis of the vagus nerve. This theory was supported by animal experiments. Furthermore, surgical vagectomy, as carried out in peptic ulcer disease, has been followed frequently by gastric dilatation.[11]

A central disturbance of the vagus nerve could be explained by the decrease of oxygen consumption[12] and glucose utilization in the brain during diabetic acidosis or coma.[13-14]

SUMMARY

Severe gastrointestinal hemorrhage occurring during and shortly after diabetic coma in a thirty-one-year-old white male required subtotal gastrectomy to control the blood loss. Macroscopic and microscopic examination of the excised portion of the stomach and the duodenal bulb did not reveal pathologic changes other than increased thickening of mucosal folds and dilatation of submucosal capillaries.

Clinical records and autopsy reports of thirty cases of diabetic acidosis or coma were reviewed with respect to gastrointestinal pathology. Possible etiologic factors leading to gastrointestinal hemorrhage are discussed.

SUMMARIO IN INTERLINGUA

Hemorrhagia Gastric in Coma Diabetic

Sever hemorrhagia gastrointestinal que occurreva in un masculo de racia blanc de trenta-un annos de etate durante e brevemente post coma diabetic requireva gastrectomia subtotal pro arrestar le perdita de sanguine. Le examine macro- e microscopic del excidite portion del stomacho e le bulba duodenal non revelava alterationes pathologic altere que le augmentate spissification del plicas mucosal e le dilatation del capillares submucosal.

Le dossiers clinic e le reportos necroptic de trenta casos de acidosis diabetic o de coma diabetic esseva scrutinate ab le puncto de vista del pathologia gastrointestinal. Es discutite le factores etiologic que es possibilemente responsabile pro le occurrentia de hemorrhagia gastrointestinal.

ACKNOWLEDGMENT

I am grateful to Dr. Howard F. Root for inspiration and assistance in the preparation of this article.

Postmortem examinations were performed in the Department of Pathology of the New England Deaconess Hospital under the direction of Dr. Shields Warren.

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Insulin-resistant Diabetic Coma

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Recently, new methods of investigation have provided studies of insulin resistance which have demonstrated considerable discrepancy of data and of interpretation. This material suggests that there may be differences between the mechanisms of resistance in patients with so-called "idiopathic" insulin resistance and those with diabetic acidosis. A basic question concerns the presence as well as effectiveness of circulating insulin or insulin-like activity in patients with insulin resistance due to diabetic acidosis. The following case demonstrates that high levels of serum insulin-like activity were found in a patient with diabetic acidosis requiring very large doses of insulin for control of the hyperglycemia.

CASE REPORT*

A sixty-eight-year-old white female was admitted to the U.S.C. Diabetes Service at the Los Angeles County Hospital in September 1958 with a diagnosis of diabetic coma. She was known to have had diabetes for eleven years and had been poorly controlled with 30 to 60 units of NPH insulin daily. Two years previously, gangrene of the toes resulted in two separate admissions for diabetic coma and acidosis. Amputation was necessary in both instances. Both episodes were controlled with nominal doses of insulin. There was no evidence of unusual insulin resistance.

The present episode followed development of a thigh abscess which had been neglected. At the time of entry she was semi-stuporous, dehydrated, and in shock, but did not demonstrate Kussmaul-type respirations. Urine sugar and acetone were four plus. The serum acetone was positive at a dilution of 1:32. The blood sugar was 1,200 mg. per 100 ml., the CO_2 combining power was less than 5 mEq./L., the serum amylase was 2,600 units/ml., the blood urea nitrogen was 49 mg. per cent, and the serum potassium was 4.4 mEq./L. Shock was treated with intravenous fluids, whole blood, and plasma. Nevertheless, Aramine Bitartrate was necessary to maintain the systolic blood pressure at 110 mm. Hg. The urine volume varied between 40 and 120 ml. per hour until the final twenty-four hours of life when the patient became progressively more oliguric.

In the first twelve hours after admission, 1,240 units of insulin were given intravenously. During this period, the blood sugar rose to 1,400 mg. per 100 ml.; and CO_2 combining power became elevated to 9 mEq./L., and the serum amylase rose to 7,600 units/ml. After this, the insulin was doubled every two hours until 10,000 units were given in each dose. It became increasingly difficult to maintain the blood pressure and she died fifty-six hours after entry. Ten minutes before death, the blood glucose was 472 mg. per 100 ml. and the CO_2 combining power was 23 mEq./L. Serum potassium had dropped to 2.8 mEq./L. four hours after entry, but was adequately controlled thereafter.

Postmortem examination revealed no abnormalities of the brain or heart. The lungs showed pulmonary edema and bilateral hydrothorax. The pancreas was normal in size and consistency and the pancreatic duct was patent. No evidence of fat necrosis was present. There was slight to moderate hyalinization of islet cells. The liver weighed 1,300 gm. and was light brown in color with a smooth capsule. Microscopic examination showed moderate fatty degeneration. The surface of the kidneys was slightly granular and there was thinning of the cortex. Thickening of the capsular epithelium was suggestive of early Kimmelstiel-Wilson disease.

Figure 1 demonstrates the changes in CO_2 combining power and blood sugar associated with the levels of insulin-like activity (log_{10} scale) and dosage of administered insulin. The total amount of insulin given was 97,740 units. Despite this large amount of insulin, the lowest blood sugar, 472 mg. per 100 ml., was not obtained until just ten minutes before death.

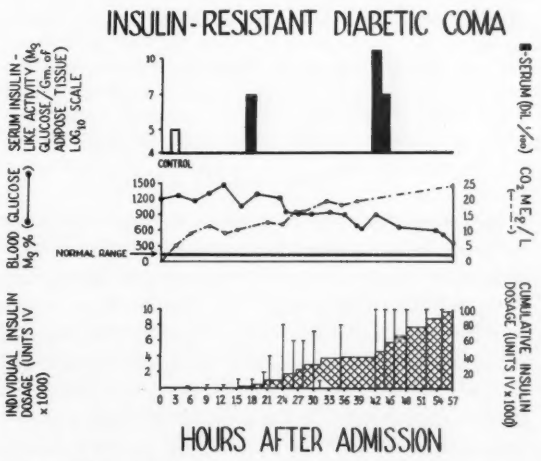
INSULIN-RESISTANT DIABETIC COMA
SERUM INSULIN-LIKE ACTIVITY (Mg GLUCOSE/Gm. of ADIPOSE TISSUE) LOG_{10} SCALE
CONTROL
SERUM (DIL. 1/100)
BLOOD GLUCOSE Mg % (———)
NORMAL RANGE
CO_2 MEq/L (- - -)
INDIVIDUAL INSULIN DOSAGE (UNITS IV x 1000)
CUMULATIVE INSULIN DOSAGE (UNITS IV x 1000)
HOURS AFTER ADMISSION

FIG. 1. Chronological sequence of insulin administration, presented as individual cumulative insulin dosage, related to blood glucose and CO_2 — combining power responses. Insulin-like activity of sera diluted 1/100 is indicated sixteen, forty-two, and forty-three hours following admission.

From the Department of Medicine, University of Southern California Medical School, and the Los Angeles County Hospital, Los Angeles, California.

* A preliminary report of this case was presented in Clin. Res. 7:63, 1959.

TABLE 1

Insulin-like activity of sera

Specimen		Insulin dosage		Determinations		Glucose uptake mg. glucose/gm. adipose tissue		Significance of differences between serum and control	
Description	Time obtained	Cumulative	Last previous dose	Serum dilutions	No. of	Mean*	SEM limits	T	P
Control (0.2% albumin)						4.6	4.1-5.1		
First serum	Sixteen hours after admission	2,540	Two hours after 800 units insulin I.V.	1/100	14	7.1	6.3-8.0	2.7	<0.01
				1/1,000	9	6.2	5.7-6.7	2.2	>0.02, <0.05
Second serum	Forty-two hours after admission	47,740	Fifteen minutes after 8,000 units insulin I.V.	1/100	16	10.1	10.0-10.2	6.4	<0.001
				1/1,000	20	9.3	8.4-9.9	5.3	<0.001
Third serum	Forty-three hours after admission	47,740	One hour after 8,000 units insulin I.V.	1/100	21	7.6	6.7-8.7	3.1	<0.01
				1/1,000	10	5.7	4.8-6.8	1.1	>0.2, <0.3
				1/10,000	15	7.3	6.5-8.2	3.0	<0.01

*Antilogs.

Three samples of sera were drawn for bio-assay of insulin-like activity. The first of these was taken sixteen hours after admission and two hours after administration of 800 units of insulin intravenously. The second was obtained forty-two hours after admission and fifteen minutes following administration of 8,000 units of insulin; and the third was secured forty-three hours after admission, and one hour after the administration of 8,000 units of insulin. There was a forty-five-minute interval between the second and third specimens. The technic of the bio-assay, utilizing glucose uptake by rat epididymal adipose tissue, has been described previously.[1] The assay results are shown in table 1 and figure 1. Significant levels of insulin-like activity were found in all samples at dilutions of 1:1,000 at least.

DISCUSSION

By the same method of insulin bio-assay, it has been demonstrated that patients with diabetic acidosis show little or no insulin-like activity in their sera before treatment, but that with insulin therapy there is a variable increase in this activity, often preceding clinical response or correction of hyperglycemia.[1] In 1956, Presland and Todd[2] reported a case of prolonged, severe insulin resistance characterized by the presence of marked plasma insulin-like activity. They ascribed this insulin resistance to defective response in the tissues. Field[3] and his co-workers have reported marked plasma insulin-like activity in a case of insulin resistance. Their studies suggested that there was an apparent failure of the patient's muscle and adipose tissue to respond to insulin. A recent case was described by Leonards and Martin[4] in which circulating insulin-like activity was demonstrated in a nonacidotic patient who was moderately resistant to insulin.

An antagonist to insulin has been demonstrated in the sera of some patients with diabetic acidosis by Field and Stetten.[5] This anti-insulin factor migrates electrophoretically with the alpha-1-globulin serum protein fraction, and disappears as therapy brings the acidosis under control. Vallance-Owen and Lukens[6] showed that the appearance of an insulin antagonist in depancreatized cats could be prevented by hypophysectomy or adrenalectomy. Subsequently, this insulin-antagonistic factor was reported to be associated with the albumin fraction of plasma.[7] Lipoprotein fractions from rat serum have also demonstrated anti-insulin activity.[8] In some instances, inhibition of insulin action has been attributed to serum gamma globulin.[9]

The present case, and the cases of Presland and Todd,[2] Field[3] and his co-workers and of Leonards and Martin[4] demonstrate that there may be insulin-like activity in the sera of some insulin-resistant diabetics, but this activity is not associated with reduction of hyperglycemia. The reasons for this apparent paradox are unknown, but it is suggested that peripheral tissue defect or alteration may be responsible for insulin resistance in these cases. There

is abundant evidence that circulating serum or plasma factors may be associated with insulin resistance, but the evidence suggesting the presence, if not the primacy, of peripheral tissue factors is becoming more prominent.[10]

SUMMARY

1. A case of a diabetic coma is presented in which the very high insulin dose of 97,740 units, given in a fifty-six-hour period, was associated with a blood glucose decline from 1,200 mg. per 100 ml. to 472 mg. per 100 ml.

2. Sera obtained from the patient during the course of insulin therapy demonstrated high levels of insulin-like activity. This insulin, or insulin-like, material was relatively ineffective in lowering the blood sugar.

3. It is suggested that a defect or alteration of the peripheral tissues of some insulin-resistant diabetics may prevent insulin from acting at the cellular level.

SUMMARIO IN INTERLINGUA

Coma Diabetic, Resistente a Insulina

1. Es presentate un caso de coma diabetic in que le altissime dose de 97.740 unitates de insulina administrate in un periodo de cinquanta-sex horas esseva associate con un reduction del glucosa del sanguine ab 1.200 a 472 mg pro 100 millilitros.

2. Specimens de sero obtenite ab le patiente in le curso del therapia a insulina monstrava alte nivellos de activitate insulinoide. Iste insulina, i.e., iste material insulinoide, esseva relativemente inefficace in le reduction del sucro de sanguine.

3. Es suggerite que un defecto o un alteration del tissus peripheric de certe diabeticos con resistentia a insulina preveni le action del insulina al nivello cellular.

ACKNOWLEDGMENT

This study was supported in part by Grant #A-1516, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service, U. S. Department of Health, Education, and Welfare. Also, a grant from the Diabetes Association of Southern California provided assistance in this study. We also thank Dr. Helen E. Martin for advice and assistance.

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Another novel approach to the definition of obesity in man has been made by Behnke. In guinea pigs, approximately 4 per cent of the lean body weight of males and 7 per cent of the lean body weight of females is fat-free adipose tissue. This normal complement of fat-free adipose tissue had a maximum capacity for lipid storage which approximates 20 per cent of body weight in the male and 28 per cent in the female. If lipid is stored in these animals beyond these limits in response to long-sustained positive caloric balance, new fat cells are formed to accommodate this fat and the fat-free "adipose tissue" increases. Apparently, macrophages and other elements of the reticulo-endothelial system assume the role of adipose tissue cells under these conditions. When this alteration in storage mechanism occurs, representing essentially a pathological change, Behnke suggests that obesity may be said to exist. It is of interest that when these data are applied to man, the lines of demarcation between the obese and nonobese (20 per cent fat in the male and 28 per cent fat in the female) correspond to increases in body weight of 13 per cent in males and 14 per cent in females beyond "desired weight," which is in agreement with the statistical definition propounded above.

From "Obesity as a Nutritional Disorder," by Robert E. Olson, in *Federation Proceedings*, Vol. 18, No. 2, Part II, p. 59, July 1959.

The Fate of the Second Leg in the Diabetic Amputee

Martin G. Goldner, M.D., New York

About 100 years ago, Marchal de Calvi[1] wrote in his first treatise on diabetic gangrene: "Often the opposite leg is affected, gangrene sets in and soon again the patient succumbs to horrible suffering. Having relieved him only of his local affliction (by amputation), I have done nothing but mutilate him." The vast newer literature on lesions of the legs and feet in diabetes testifies to their continued high incidence, seriousness and poor prognosis, but rarely refers to the bilateral lesions.[2-5] Yet, the fate of the second leg is intimately related to that of the first leg. Ulcers and gangrene of feet or toes, though precipitated by trauma or other exogenous factors, result from systemic vascular and nervous diseases complicating diabetes. When unilateral lesions call for medical attention, one may well expect involvement of the second leg even though it may appear asymptomatic. The fate of the second leg may reflect the further natural course of the disease; it may be modified by the treatment awarded to the unilateral lesions; and it may deserve serious consideration in deciding on such treatment plan. Evidently there is need for information on this aspect of the complications of diabetes.

As part of a study on peripheral vascular disease in diabetes, we have attempted therefore to assess the integrity or impairment of the second leg in those patients who were admitted to the Jewish Chronic Disease Hospital with unilateral leg lesions or amputations. The study is still in progress, yet a preliminary report on the findings in a first group of admissions during an eighteen-month period appears to be warranted.

OBSERVATIONS

There were seventy-one patients. Their age, sex distribution and the time of the development of the first leg lesion in relation to the duration of their diabetes are shown in figure 1, which demonstrates the following:

The sexes were represented almost equally: thirty-nine males and thirty-two females. There was a difference

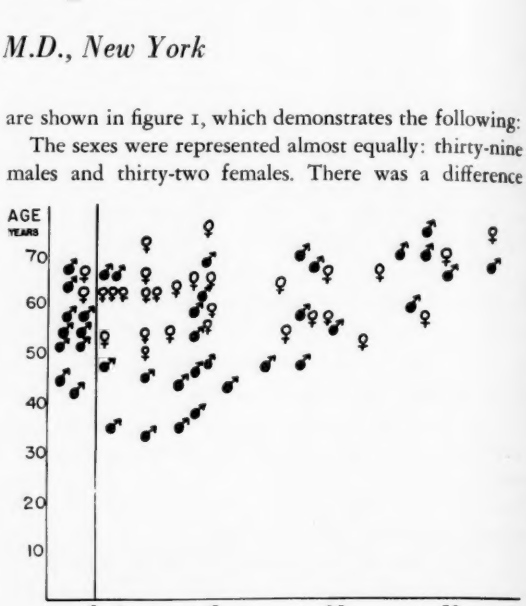

FIGURE 1

between the sexes in the age at onset of the leg lesions. The females were fifty years or older, while fourteen males were younger than fifty years. All patients suffered from "maturity-onset" diabetes. Although one expects that forty years after the discovery of insulin, enough juvenile diabetics have reached the age in which vascular lesions of the legs are common, there was no patient in our series with onset of the disease under the age of twenty years.

The leg lesions were related to the age of the patients rather than to the duration of their diabetes. Twelve of the seventy-one patients, i.e., almost 20 per cent, had developed their first leg lesions prior to the recognition of their diabetes. This is a rather surprising finding, but it is in line with recent similar observations like that of Bartels and Rullo,[6] who carried out routine glucose tolerance tests in 100 patients with peripheral vascular lesions, and discovered twenty unsuspected diabetics. Long ago, Marchal de Calvi[1] found similarly that "It is remarkable in how great a number of cases it is the leg lesion, the gangrene, which reveals to the physician the presence

Presented at the Nineteenth Annual Meeting of the American Diabetes Association in Atlantic City on June 6, 1959.

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of the disease which without this complication may often remain indefinitely undiagnosed."

The histories of these seventy-one patients with leg lesions showed rather interesting data with regard to management of diabetes and its complications. These are illustrated in table 1. Twenty patients had followed no regimen at all; thirteen followed dietary restrictions only; twenty-six were under insulin treatment, and twelve were for some time during the past three years under treatment with oral hypoglycemic agents, particularly tolbutamide. Control of diabetes was poor in thirty-three patients, and could be described as fair in thirty-eight. We considered the control as fair if the urinalyses were reported as negative, or only occasionally 1+ or 2+ positive, and if the fasting blood sugar was at no time higher than 150 mg./100 ml. General well-being of the patients and their weight equilibrium were used as additional criteria where the information on blood and urine examinations was inadequate. Patients with frequent bouts of severe glycosuria, with fasting blood sugar levels above 150 mg./100 ml., or those who reported great fluctuations in their weight and their well-being, were considered as poorly controlled. There was no instance of diabetic coma, but as might be expected, there was a large number of other complications, such as neuropathy, nephropathy and retinopathy. An analysis and correlation of these complications to the diabetes and the leg lesions will be presented in another context.

TABLE 1

The diabetic history of seventy-one patients with unilateral leg lesions and subsequent involvement of the other leg

Onset	
Growth	0
Maturity	71
Management	
Free	20
Diet	13
Insulin and diet	26
Oral agents and diet	12
Control	
Fair	38
Poor	33
Complications	
Acidosis, coma	0
Retinitis	58
Nephropathy	26
Neuropathy	45

Of the seventy-one patients, forty-one had previously undergone unilateral amputations; thirty had been treated conservatively. In thirty-six of the unilateral amputees the new lesion involved the other leg; in five the other leg appeared intact, but the amputation stump was involved. Of the thirty patients without previous amputations, nine showed lesions of both legs at the time of admission, and two developed ulcerations of the other leg while under treatment for the contralateral lesion. Thus, forty-seven patients of a group of seventy-one consecutive admissions with diabetic gangrene or amputation of one lower extremity showed involvement of the other leg. The new lesions were ulcers or gangrene of the forefoot in twenty-three cases; of forefoot and heel in seventeen, of heel alone in four and of the lateral aspect of the foot in three. Twenty-six cases showed involvement of bone by osteomyelitis. Of the remaining twenty-four cases without visible involvement of the second leg, sixteen were entirely asymptomatic, and ten stated on questioning that they noticed coldness and weakness of the remaining leg (table 2).

The interval since the first leg lesion is shown in figure 2. Eleven patients had developed the lesion of the second leg within one year; in two the second lesion developed while under treatment for the contralateral lesion; eighteen within two years; five within three years; six within four; three within five; and four after

TABLE 2

The fate of the other leg in seventy-one diabetic patients with previous unilateral leg lesions

No symptoms		14
Symptomatic		57
Without visible lesions	10	
Involvement of forefoot	23	
Involvement of forefoot and heel	17	
Involvement of heel	4	
Lateral aspect of foot	3	
Complicated by osteomyelitis	26	

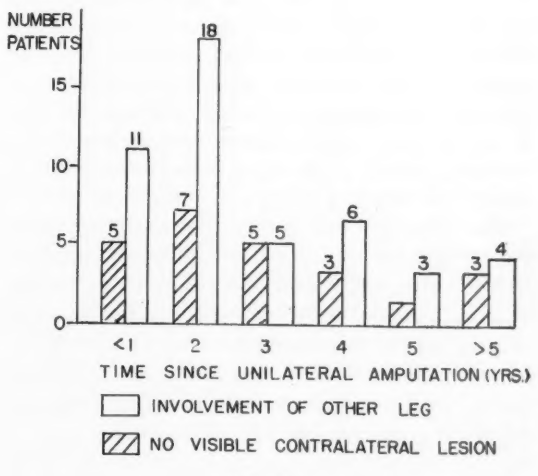

FIGURE 2

more than five years. Thus, in 50 per cent of the patients, the lesions of the second leg had developed within two years after the involvement of the first leg. This figure would probably be still higher if one considers that thirteen patients without visible lesions of the second leg had experienced their first leg lesion within the recent past, a period shorter than two years. Only three patients had preserved an apparently intact second leg for more than five years. Even in the second leg without visible lesions and without significant symptoms, circulatory impairment was found without exception by oscillometric examinations.

The generalized vascular involvement in the diabetic patients with lesions of the leg is well known by the frequent occurrence of vascular disease in other areas of the body, as retinopathy, nephropathy and cerebral arteriosclerosis with cerebral vascular accidents. An attempt was made to evaluate the functional reactivity of the vessels of the fingers and the hand, areas which show clinical involvement only rarely. Twenty patients were examined by the method of Sigroth:[7] The foot was immersed in warm water and the response of the skin temperature of the fingers of both hands was recorded. Normally, there occurs after a period of latency a rapid rise of the skin temperature of the fingers which reaches a maximum of 35° C. within thirty-five to forty minutes. In all our patients, a decreased reactivity was found which manifested itself both in a prolonged period of latency and an inability to attain end temperatures of more than 32° C. This finding is in line with the plethysmographic studies of the fingertips by Megibow and others[8] and with the studies of the arterial pulse wave of Lax and others.[9] In spite of the rarity of symptomatic lesions of the hands or other acra, we encountered in five patients the "stiff and pale hands" of the diabetic to which Lundbaek[10] has called attention, twice associated with Dupuytren-like contractures of the palmar fascia, and once with gangrene of the scrotum, probably traumatically induced by an indwelling catheter. This lesion healed under conservative therapy with vasodilator and antibiotic medication.

The ultimate fate of the second leg in our patients was far from satisfactory (table 3). Only fifteen of the forty-seven patients responded to conservative management. Amputations of the second leg became necessary in thirty-two. In fourteen patients only part of the foot needed to be sacrificed, so that they retained their leg, though impaired; eighteen became double amputees. All of these patients had been under medical supervision, at least since their first leg lesions; they had been instructed in proper hygiene and advised in diabetic management; they had been treated with various vasodilator drugs by the oral, intravenous and intra-arterial route; some had undergone sympathectomy; and most had been fitted with modern prostheses and had taken advantage of the modalities of physical medicine and rehabilitation. Yet, their vascular complication progressed to bilateral leg involvement, and all too often to the loss of the second leg. In this group of patients with maturity onset diabetes, no definitive correlation was apparent between the progression of the vascular complication and the duration or degree of severity or control of the diabetes itself. This observation calls vivid attention to the great need for better means and new approaches to the management of the vascular lesions of diabetes, and for better understanding of their etiology. One hundred years ago, the question was raised by Marchal de Calvi, to quote him again: "Is it not possible that the stressful life of our times, with its struggle, aggression and anxiety which overtax all our emotional strength, has contributed to the greater frequency of certain diseases, among them diabetes and its complications?" Today we are still searching for a conclusive answer, which may enable us to find a way to prevent these serious complications.

TABLE 3

The ultimate fate of the second leg (forty-seven cases)

Conservative treatment		15
Amputation		32
Above knee	10	
Below knee	8	
Resection of toes or forefoot	14	

SUMMARY

1. The second leg of the unilateral diabetic amputee shares the fate of the first rather often and relatively soon.

2. Current diagnostic and treatment modalities do not seem to have altered this fate significantly.

3. Bilateral, as well as unilateral, diabetic leg lesions may develop prior to the other manifestations or recognition of the diabetes itself, and occur almost as often in the mild as in the severe disease, and under fair or poor control. Neither the severity of diabetes nor its control seems to be the main determining factor in the development of leg lesions.

4. The demonstration of vascular impairment in the hands of diabetic patients with leg lesions gives further evidence of the systemic nature of this complication.

SUMMARIO IN INTERLINGUA

Le Destino del Secunde Gamba in le Amputato Diabetic

1. Le secunde gamba del unilateralmente amputate diabetico ha satis frequentemente e relativemente tosto

le mesme destino como le prime.

2. Le currente modalitates diagnostic e tractamental non pare haber alterate iste facto significativemente.

3. Diabetic lesiones de gamba, bilateral si ben como unilateral, pote disveloppar se ante omne altere manifestationes o mesmo ante le recognition del diabete mesme; illos occurre in leve casos del morbo quasi tanto frequentemente como in casos sever e in casos de adequate regulation si ben como in casos mal regulate. Ni le severitate de diabete ni le grado de su regulation pare esser le principal factor determinatori in le disveloppamento del lesiones de gamba.

4. Le demonstration de difficultates vascular in le manos de patientes de diabete con lesiones de gamba representa un prova additional pro le natura systemic de iste complication.

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Falls a Major Cause of Death

Accidental falls are a major cause of mortality in the United States, accounting for more than 20,000 deaths a year, or a death rate of twelve per 100,000 population. The loss of life resulting from falls is more than three times that caused by fires and explosions, nearly ten times that from accidents involving firearms, and about fifteen times the toll from aircraft accidents.

Somewhat over half of the people fatally injured in falls—about 11,000 a year—sustain their injuries in and about the home. This large proportion reflects the relatively high frequency of falls among older people, who generally spend a major part of their time at home. About 1,000 fatal falls each year take place on streets and highways, and lesser numbers occur in public buildings, in places of recreation and sport, on farms, and in industrial places. It should be noted, however, that only 2 per cent of all fatal falls—little more than 400 a year—result from accidents in factories, mines and quarries, and other industrial places.

Falls from ladders account for at least 300 deaths a year. The majority of these fatalities occur in and about the house, males comprising nine tenths of the victims. Approximately 3,800 deaths annually are attributed to falls out of windows, from roofs, trees, chairs, beds, and to other falls from one level to another.

Nearly 4,000 deaths annually are reported as due to falls on the same level—on the floor, ground, sidewalk, street, and the like. Nearly nine tenths of the people reported as fatally injured in falls on the same level are sixty-five years of age and older.

The death rate from falls decreases moderately from infancy to a minimum at the school ages and then rises progressively with advance in age, slowly at first but very sharply at the older ages. The concentration of the mortality from falls in later life is much more pronounced for females than for males. In fact, under age seventy-five the death rate is higher for males than for females in each color group, but thereafter the sex ratio of the mortality is sharply reversed. Nonwhite persons generally have a higher mortality from falls than the white until the older ages.

There is little doubt that the toll from accidental falls can be reduced. One way to prevent such accidents is to keep the house in good repair; even slight variations in walking surfaces may cause slips or missteps, especially among the aged. Illumination should be adequate and light switches properly located. Additional attention needs to be focused on personal factors contributing to falls, such as undue haste, faulty judgment, and physical limitations.

From *Statistical Bulletin*,
Metropolitan Life Insurance Company,
Vol. 40, pp. 8-10, April 1959.

Severe "Juvenile" Diabetes of Thirty-nine Years' Duration

A Case Report

Emery C. Miller, Jr., M.D., and William J. Reeves, M.D., Winston-Salem

Since insulin did not become generally available until 1923, reports of cases of diabetes of thirty-five years' or more duration have only recently appeared in the literature. West[1] reported a case and Root and Barclay[2] were able to document thirty-five or more years' duration in ninety-six patients out of a group of 34,000 known diabetics. Twenty-one of these patients had onset of diabetes under age twenty-five. Postmortem findings were available in six. Hagedorn notes on follow-up study of the first eight Danish diabetic patients treated with insulin in 1923 that five are still alive, with an average duration of diabetes of forty-one years. Four of these have normal vision.[3] This paper reports an autopsied case with onset of diabetes at age twenty and thirty-nine years' proved duration.

CASE REPORT

The family history was positive in that the patient's father, a physician, developed diabetes at age fifty-eight. In September 1919, the patient, a twenty-year-old college athlete, developed a scalp abscess followed by severe acidosis and great loss of carbohydrate tolerance, polydipsia, polyuria, and generalized weakness. Initial regulation was by severe dietary restriction. His daily diet on discharge from the New England Deaconess Hospital consisted of 42 gm. carbohydrate, 44 gm. protein and 77 gm. fat. Insulin therapy was begun in November 1922, and the patient continued to take Regular Insulin three or four times daily throughout the remainder of his course. For one period of approximately eight years he additionally took some Protamine Zinc Insulin every morning. The patient was never in acidosis after insulin therapy was begun. Severe hypoglycemic reactions with unconsciousness occurred once or twice per year on the average. Frequent minor hypoglycemic episodes characterized his course, particularly in the last decade of his life.

The patient gauged his ante-cibal Regular Insulin dosage by what he expected to eat at that meal. His daily insulin requirement was 80 to 120 units. Diet was not routinely weighed or measured. At the time of death he was approximately twenty pounds over his ideal weight.

From the Departments of Medicine and Pathology of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.

At age fifty-eight the patient was hospitalized with a four-week history of substernal tightness and paroxysmal nocturnal dyspnea. He had continued his work as a physician despite his symptoms until he experienced an unusually severe bout of substernal pain and was found to have electrocardiographic evidence of recent posterior myocardial infarction. Pertinent physical findings included a blood pressure of 160/88 mm. Hg., no cardiac enlargement or murmurs, scattered râles at both lung bases posteriorly and one plus pitting edema of the lower extremities. The ophthalmologist reported a "few peripheral punctate hemorrhages (*micro-aneurysms? Ed.*), and no exudates" in the fundi. Knee jerks were equal and active bilaterally. There was no impairment of sensation to light touch or pin prick. Dorsalis pedis, posterior tibial, popliteal, femoral, and radial pulses were palpable.

Accessory clinical findings of interest included slight left ventricular enlargement by X ray. The aorta was elongated and slightly tortuous. Serial electrocardiograms showed little change from the pattern of a recent posterior infarction. Fasting blood sugars up to 242 mg. per 100 ml. were obtained immediately after hospitalization, but adequate control was soon achieved. Total serum cholesterols measuring between 312 and 342 mg. per cent were recorded. Total serum protein was 6.3 gm. per 100 ml., with albumin 3.2 gm. and globulin 3.1 gm.

Repeated routine urinalyses were negative for protein. There were two to five white blood cells present in microscopic examinations of the urinary sediment. Specific gravity of a random sugar-free urine specimen reached 1.027. The blood urea nitrogen was 24 mg. per cent. Unfortunately, no more precise evaluation of renal function was carried out, clinical interest being focused on the cardiac problem.

The patient was treated by weight reduction, rest, sodium restriction and digitalization, but continued after discharge to have recurring episodes of acute left ventricular failure and moderately severe angina with minimal exertion. It may be of interest that the patient was entirely convinced that anginal episodes were more common at times of hyperglycemia and would on occasion attempt to control pain by injecting himself with Regular Insulin.

At age fifty-nine, one year after the onset of cardiac symptoms, he developed severe chest pain shortly after breakfast one morning and expired two minutes later.

Autopsy revealed myocardial hypertrophy with marked myocardial fibrosis. The heart weighed 590 gm. There was moderate aortic atherosclerosis and an old subendocardial myocardial infarct. Atherosclerosis of the coronary vessels was marked. There was encroachment upon the lumina of the

vessels, but no thrombi were found in any of the coronary arteries. In addition there was minimal pulmonary atelectasis, emphysema and fibrosis, and moderate pulmonary arteriosclerosis. There was minimal focal pancreatic fibrosis. The number of islets of Langerhans seemed to be decreased in the two sections studied. The cause of death in the patient could not be determined on an anatomical basis but it was surmised that the patient had died of cardiac arrhythmia secondary to his marked coronary atherosclerosis.

Except for the sclerotic changes noted in the vessels there was a striking absence of the changes usually seen in diabetes of this known duration. Flat preparations of the retina were not obtained, since permission to examine the head was not given. Figure 1 is a photomicrograph of the kidney in which only minimal evidence of intercapillary glomerulosclerosis could be found.

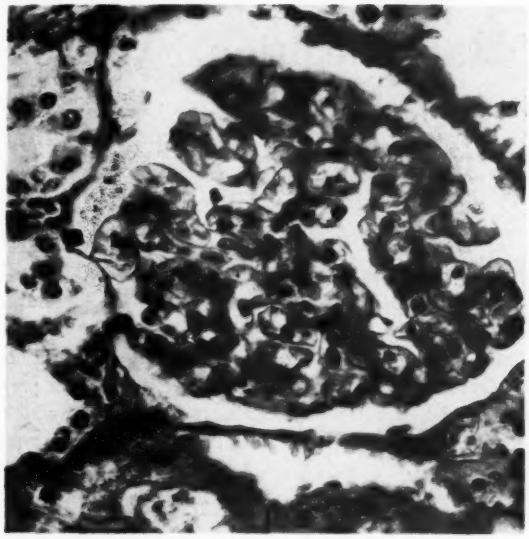

FIG. 1. Typical glomerulus, hematoxylin-eosin stain. x480.

SUMMARY

A case of severe "juvenile" diabetes of thirty-nine years' documented duration is presented. The kidneys at autopsy showed minimal evidence of intercapillary glomerulosclerosis. The patient's diabetes was well controlled by the use of Regular Insulin three or four times per day for nearly thirty-six years. The case is presented as evidence for the view that the small blood vessel damage so characteristic of juvenile diabetes of long duration may be minimized and indefinitely postponed by long-term careful control of diabetes.

SUMMARIO IN INTERLINGUA

Sever Diabete "Juvenil" de un Duration de Trenta-Novem Annos: Reporto de un Caso

Es presentate un caso sever de diabete "juvenil" con un duration documentate de trenta-novem annos. Al necropsia le renes exhibiva evidentia minimal de glomerulosclerosis intercapillar. Le diabete del patiente habeva essite ben regulate per le uso de Insulina Regular tres o quatro vices per die durante quasi trenta-sex annos. Le caso es presentate como prova in supporto del opinion que le lesiones del micre vasos de sanguine que es si characteristic de diabete juvenil de longe duration pote esser reducite e retardate indefinitemente per le caute regulation a longe vista del condition diabetic.

ACKNOWLEDGMENT

Clinical records concerning this patient were very graciously made available to us by Dr. Elliott P. Joslin and Dr. Howard F. Root of the Joslin Clinic, Boston, Massachusetts, and by Dr. Ernest H. Yount, Jr., and Dr. C. Glenn Sawyer of the Bowman Gray School of Medicine, Winston-Salem, North Carolina.

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More recently evidence has begun to accumulate that the type of carbohydrate in the diet has an effect on the amino acid requirement. M. W. Marshall and M. Womack (*Nutrition Reviews 12*:182, 1954) found that when adult rats were fed a purified ration containing each of the essential amino acids at a level of 0.1 per cent, the animals on the sucrose ration lost 28.8 mg. of nitrogen per day while those on the dextrin ration lost only 15.5 mg. Adding glutamic acid or increasing the level of the essential amino acids to 0.2 per cent improved nitrogen balance but, in both cases, the animals on the dextrin ration did better than those on the sucrose.

From *Nutrition Reviews*, Vol. 17, No. 4, p. 107, April 1959.

Malabsorption Syndrome and Diabetes Mellitus

Emil P. Taxay, M.D., Stuart Roath, M.D., and Stanley Mitchel, M.D., Miami

INTRODUCTION

Diabetic *steatorrhea* has only recently been described[1-8] and no cases of primary *malabsorption syndrome* associated with diabetes could be found in the literature. Two suggestive cases have been reported.[4,5] The present confirmed case of diabetes and primary malabsorption syndrome may be unique. Furthermore, the patient presented with hemorrhagic complaints on admission, which is infrequent in patients with the malabsorption syndrome.

CASE REPORT

Present illness. A thirty-two-year-old diabetic female was admitted to the hospital on Jan. 2, 1959, complaining of painful hemorrhages into the soft tissues of the thighs for five days, hematuria with passage of clots for two days, and epistaxis and melena for one day. She also suffered from weakness, dyspnea and palpitations.

Past history. At the age of nineteen years her condition had been diagnosed as diabetes mellitus, after a history of weight loss, polyuria and polydipsia. Since that time she had taken various insulin preparations and, though rarely rigidly controlled, had never had an episode of acidosis or insulin reaction. Several months after the diagnosis of diabetes she had her first recorded episodes of diarrhea. These episodes, which she had at two- to three-month intervals, lasted two to three weeks and were characterized by the passage of three to ten watery, relatively inoffensive stools daily. The stools were not accompanied by abdominal cramps nor were they described as being bulky or containing blood or mucus. Nocturnal incontinence of stool occasionally occurred. She never gained her original weight (maximum prediabetic weight unknown) and ceased to menstruate in about two years, after a period of oligomenorrhea.

At the age of twenty-two, in 1949, she was admitted to a hospital for the first time for investigation of this diarrhea. Physical examination at that time showed her to be a poorly nourished, cachectic individual, weighing about 100 lb. (height 5 feet 2 inches). On examination she was otherwise unremarkable.

Small bowel studies were "compatible with various insufficiency diseases" and her bones were radiologically osteoporotic. Duodenal drainage showed low trypsin and normal amylase. During this admission her diabetes was regulated; she was given a milk-free diet and placed on pancreatin, liver extract and Monotan (a detergent). Her diarrhea did not abate and she was discharged after forty-nine days (the laboratory data will be found in table 1).

She continued without change in her symptom complex until 1952, when she was readmitted with an ulcer of the leg

From the Department of Medicine, University of Miami School of Medicine, Miami, Florida.

TABLE 1

Date	1949	1952	1957	1958	1959
Age	22	25	30	31	32
Weight	100 lb.				90 lb.
Hb.	11 gm.%	11.5 gm.%	7 gm.%	11.7 gm.%	4.4 gm.%
W.B.C.	Normal				Normal
Prothrombin time		15 sec.	153 sec.	17 sec.	300 sec.
Total protein	4.2-5.6 gm.%	5.9 gm.%	3.9 gm.%	4.9 gm.%	4.4 gm.%
Albumin	2.4-3.2 "	3.3 "	3.1 "	3.9 "	1.96 "
Globulin	1.8-2.4 "	2.6 "	.8 "	1.0 "	2.48 "
Cholesterol	114-140 mg.%	143 mg.%			220 mg.%
Alk. phosphatase	15 K.A.	6.6 B.U.			8.5 B.U.
Ceph. Floc.	Neg.	2+		Neg.	2+
T. Turb.	4.8	3.6			
B.S.P.	Neg.				
Bilirubin					1.50 mg.%
BUN	10 mg.%	10 mg.%			10.1 mg.%
Calcium	8.1-8.4 mg.%	9.5 mg.%			8.5 "
Phosph.	3.8-4.6 "				2.5 "
17-keto.	7 mg./24 hr.				
Stools	Neg. for blood				4+ for blood
Ova & par.	Neg.				Neg.
Stool fat	30 gm.% (dry wt.)	? Normal			60 gm.% (dry wt.)
Chest X ray	Normal				Normal
U.G.I. series	Deficiency pattern				Deficiency pattern
G.T.T.	Diabetic				Abnormal
Vitamin A					34 μg./100 ml.

of two months' duration. On physical examination, findings were essentially as before, but in addition it was noted that her fingers were clubbed and she had mild edema of the legs and hemorrhoids. Laboratory details of this second hospitalization are in table 1.

A small bowel series was reported as "suggestive of sprue syndrome." While in the hospital her leg ulcer healed on local therapy, bed rest and control of diabetes. The diarrhea continued.

In 1957 she was admitted to a second hospital (third hospitalization) with hematuria. Radiographic and functional urinary tract studies were normal. Her prothrombin time was 153 seconds. Bleeding, clotting and clot retraction studies were normal. The total serum proteins were 3.9 gm. per cent. The hematuria subsided after vitamin K and blood transfusions.

A hemorrhoidectomy was peformed in 1958 without incident: Her prothrombin time was normal without specific therapy (fourth hospitalization).

She continued to have intermittent diarrhea, failed to gain weight and had been unable to work for the past two years. Her diabetes had been fairly well controlled with 50 to 60 units NPH insulin daily.

Physical examination (present admission, fifth hospitalization). The patient was a small, thin woman, looking older than her stated age. She was obviously distressed, dyspneic and sweating, and was bleeding from the nose. Her temperature was 102° F., pulse 140 per minute and her blood pressure 100/40 mm. Hg. She had fresh hemorrhages into her skin and her fingers were clubbed. Examination of the chest, heart, central nervous system and abdomen showed nothing remarkable. There was no evidence of degenerative vascular disease.

Her hemoglobin was 4.4 gm. per cent; the red blood cells were normochromic and normocytic. The urine was free of sugar, acetone and albumin but was loaded with red cells. A prothrombin time (Quick one-stage) was over five minutes. There was no evidence of a circulating anticoagulant and the fibrinogen level was 239 mg. per cent. The nonprotein nitrogen was 23 mg. per cent and the blood sugar 230 mg. per 100 ml. The stool was positive for occult blood when tested with guaiac. The patient was given 5 units (500 cc. per unit) of whole blood and ceased to bleed from the nose before the first unit had been completely infused.

Her course in the hospital was one of uninterrupted recovery from her hemorrhagic episode. The prothrombin time was nineteen seconds (normal fourteen) on the day after admission. It was normal on the fifth hospital day. There was a transient elevation of the serum bilirubin which did not persist after the seventh day.

The diarrhea persisted during her hospital stay, the stools varying from liquid to a greasy, semisolid gray-green. They were frequently lighter than water.

Gastric analysis yielded free acid and gastric biopsy disclosed normal mucosa. A secretin test gave the following results:

Volume—4.2 ml./kg.—(normal 2 ml./kg. or more)

Amylase—21 units/kg.—(normal 6 units/kg. or more)

Bicarbonate concentration—87 mEq./L.—(normal 90 mEq./L.)

The serum amylase during this test was:

Start	Two minutes	Eighty minutes
210 units	147 units	308 units

A Schilling test revealed 15 per cent excretion of B_{12} in twenty-four hours. Triolein fat absorption was less than 1 per cent within six hours.[6] Oleic acid uptake was less than 2.1 per cent in six hours.[7] These findings are consistent with a state of gastrointestinal malabsorption. Additional laboratory data may be found in table 1 and figures 1 and 2.

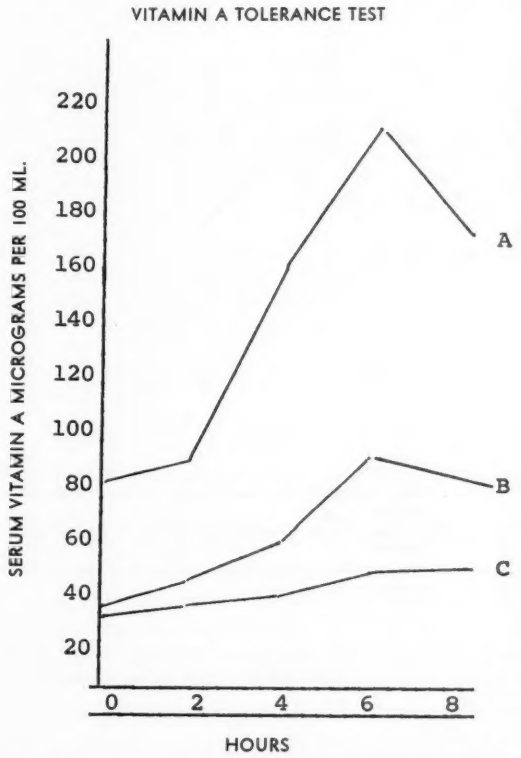

FIG. 1. A. Average of ten healthy patients with normal absorption.
B. Patient under discussion.
C. Typical curve in sprue syndrome.

Eight attempts at jejunal biopsy by the Crosby capsule technic were unsuccessful. A four-week trial on Nilevar caused no gain in weight, which remained at 93 pounds. When the patient was discharged she was hematologically stable but there had been no improvement in her diarrhea.

Although the patient's insulin requirements have increased gradually over the years, latterly she has maintained herself on a daily dosage of about 50 units of NPH. She varies this dosage somewhat depending upon how she feels, decreasing it when the diarrhea is troublesome and increasing it when she eats more heavily. She is on a 2400-calorie diet with minimum fat and a daily dose of 30 mg. of Mephyton. She finds that less vitamin K analog results in purpura. A trial of pancreatin and steroid had no clinical or laboratory effect. The patient's diabetic symptomatology has not progressed clin-

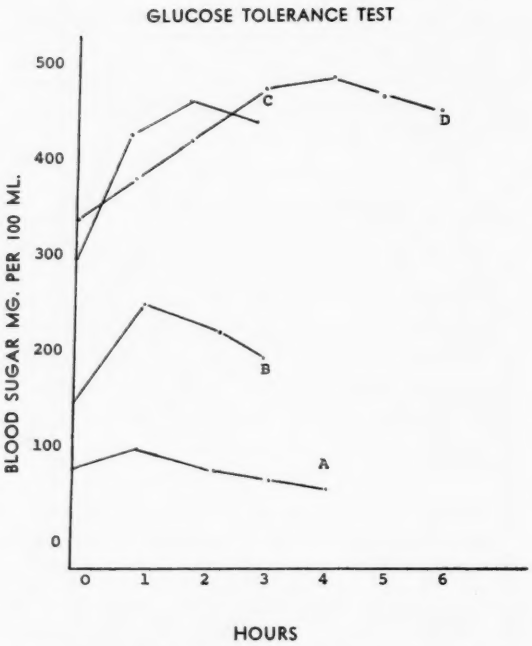

FIG. 2. A. Typical curve in malabsorption (sprue) syndrome.[13]
B. Mean glucose tolerance curves in pancreatic steatorrhea.
C. A patient with pancreatic steatorrhea and diabetes mellitus.
D. Patient under discussion during a six-hour glucose tolerance test.

ically and she is able to work a forty-hour week without difficulty. The steatorrhea (and diarrhea) remain unchanged.

DISCUSSION

Although diabetic diarrhea and steatorrhea with and without neuropathy have been described, no unequivocal cases of coexisting primary malabsorption syndrome and diabetes could be found in the literature. The current case fulfills the requirements for being considered a case of "primary" malabsorption syndrome (associated with diabetes) inasmuch as none of the established etiologies was present.[9] The following have been cited as being ultimately responsible for intestinal malabsorption:[10,11]

1. Abnormal bacterial activity or species
2. Exogenous deficiency disorder
3. Cellular—metabolic disorder
4. Decreased or altered intestinal secretions
5. Inadequate mixing of food and ferments
6. Items 1, 4 or 5 due to mechanical disorders

In our case a cellular-metabolic dysfunction due to diabetes could have been responsible for the malabsorption syndrome. The question of the clinical frequency with which diabetes and the malabsorption syndrome are associated deserves closer scrutiny as does their possible etiologic relationship.

A hemorrhagic tendency is frequently described in malabsorption states[12] and there seems to be no reasonable doubt that this is due to hypoprothrombinemia secondary to failure of prothrombin synthesis. The correction of the defect by vitamin K makes it probable that poor absorption of this essential cofactor is the real cause of the hypoprothrombinemia.

Whereas massive bleeding in the malabsorption syndrome is comparatively rare, it should always be borne in mind that the prothrombin time is frequently prolonged and the danger of hemorrhage warrants intermittent determinations of the prothrombin time. The prothrombin time might also give some idea of the efficacy of the therapy which is being used for the control of the malabsorption syndrome.

SUMMARY

A case of malabsorption syndrome associated with diabetes is presented. Of additional interest is the fact that the patient's initial complaint was in reference to hypoprothrombinemic hemorrhages, an unusual way for a malabsorption syndrome to bring itself to the clinician's attention.

Note: Since submission of this paper for publication two reports on this topic have come to our attention. One is by Green and Wollaeger, published in the *Proceedings of the World Congress of Gastroenterology*, June 1959, which describes three diabetics with coincident nontropical sprue. The other is by Ellenberg and Bookman (Max Ellenberg, M.D., and John J. Bookman, M.D.: Diabetic diarrhea with malabsorption syndrome. Diabetes 9:14-19, 1960), which describes two diabetics with malabsorption syndrome and speculates that the malabsorption syndrome may be etiologically related to the diabetes.

SUMMARIO IN INTERLINGUA

Syndrome de Malabsorption e Diabete Mellite

Es presentate un caso del syndrome de malabsorption associate con diabete. Es additionalmente interessante le facto que le gravamine initial del patiente esseva hemorrhagias hypoprothrombinemic. Isto es inusual como forma in que un syndrome de malabsorption attrahe le attention del clinico.

Depost le submission del presente articulo al redactoro, duo reportos relative a iste thema ha essite portate a nostre attention. Le un es per Green e Wollaeger, publi-

cate in le *Actos del Congresso Mundial de Gastroenterologia,* junio 1959, e describe tres diabeticos con coincidente sprue nontropic. Le altere es per Ellenberg e Bookman, "Diarrhea Diabetic con Syndrome de Malabsorption," DIABETES 9:14-19, januario-februario 1960, e describe duo diabeticos con syndrome de malabsorption. Iste ultime articulo suggere le possibilitate que le syndrome de malabsorption in le patientes presentate es relationate etiologicamente a diabete.

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The clinical definition of obesity must necessarily be arbitrary. Since depot fat is a physiological constituent, the problem centers around the question of how much body fat is too much. In young adults in the third decade, about 12 per cent of the body weight of the male and about 19 per cent of the body weight of the female is depot fat. The distribution of body weights in healthy adults is always skewed toward the high side, the skew becoming more prominent in older populations as the prevalence of obesity rises. A normal distribution is approached although not reached in young adults twenty to twenty-nine years of age. If one inspects the distribution curves for both males and females in this age group below the median values, one finds that 47.5 per cent of this half, i.e., the population encompassed by two standard deviations below the median, varies in weight from 12 to 18 per cent below the median value. If, then, one assumes that a similar distribution on the high side of the median would exclude the obese individuals present in this young population, one could conclude that an increase in weight of 15 per cent above "desired weight," i.e., median weight at age twenty-five, would occur by chance only one out of twenty times in a "normal" population, and might be considered the line of demarcation between the nonobese and the obese. This also assumes that differences of build, bone size and muscularity would be randomized in large populations which is probably not entirely true. In appraising an individual, specific corrections could be applied for these parameters. In "standard" individuals in the third decade, a 15 per cent increase in body weight would correspond to an increase in body fat from 12 to 22 per cent in males, and from 19 to 29 per cent in females. If one accepts the 5 per cent probability level as significant, these increases in body weight and body fat might be considered to be the statistical line defining obesity in the average man or woman.

From "Obesity as a Nutritional Disorder," by Robert E. Olson, in *Federation Proceedings,* Vol. 18, No. 2, Part II, pp. 58-59, July 1959.

Severe Hypoglycemia Caused by Chlorpropamide

Robert D. Lindeman, M.D., Syracuse

Chlorpropamide (Diabinese), a sulfonylurea compound chemically similar to tolbutamide, was introduced for clinical use in 1958. Early reports[1-6] indicated its usefulness and probable safety as an oral hypoglycemic agent. Hypoglycemic symptoms in diabetic patients rarely occurred on daily doses of less than 1 gm. and when present were usually mild, responding readily to oral or intravenous glucose administration. However, a patient recently was reported with severe, recurrent hypoglycemic shock following chlorpropamide administration in the usual therapeutic doses.[7] The following report is of a similar experience in a diabetic patient.

CASE REPORT

K.G., a fifty-five-year-old white male, 5′ 5″ tall and weighing 132 lb., visited his physician in July 1958, complaining of "drowsiness" and routine urinalysis revealed the presence of glycosuria. An oral glucose tolerance test showed a fasting blood glucose level of 102 mg. per 100 ml., a one-hour level of 163 mg., a two-hour level of 230 mg., and a three-hour level of 163 mg. Two and three plus glycosuria were present at two and three hours respectively. In mid-August, before any therapeutic program for diabetes could be well established, the patient suffered a posterior myocardial infarction complicated by severe hypotension and pulmonary edema. The patient was digitalized and has been maintained since on digoxin 0.5 mg. daily. In November 1958, an 1800-calorie diabetic diet and 1 gm. of tolbutamide daily were started. He was found to be hypertensive with initial systolic pressures of 160 mm. and diastolic pressures of 100 mm. and was started on reserpine 0.1 mg. three times daily. Follow-up fasting blood glucose ranged from 105 to 125 mg. per 100 ml.

The patient returned to work as an elevator operator but claimed disability because of his heart condition. In June 1959, he was dismissed from his job. On July 14, 1959, he entered the Syracuse Psychiatric Hospital in a state of profound depression.

On physical examination, the patient appeared depressed, with mask-like facies, showing a lack of spontaneous activity and speech. His arterial pressure was 115 mm. systolic, 75 mm. diastolic and pulse was 78 and regular. The heart and lungs presented no unusual findings. Positive findings were limited to the presence of kyphoscoliosis of the upper thoracic spine and a positive Babinski sign and absent Achilles reflex on the right. (These findings were apparently residual from a spinal deformity operated on shortly after birth.)

Examination of the blood revealed hemoglobin 16 gm. per 100 ml.; leucocytes numbered 8,700 with seventy-one neutrophils, twenty-five lymphocytes, three monocytes, and one eosinophil. Urinalysis was unremarkable. The fasting blood glucose was 121 mg. per 100 ml.* and nonprotein nitrogen was 40 mg. per 100 ml. The electrocardiogram showed nonspecific ST and T wave abnormalities and the chest X ray showed incomplete segmentation of two thoracic vertebrae and resultant kyphoscoliosis.

The subsequent course of events is summarized in table 1. On July 15, chlorpropamide 500 mg. daily was substituted for tolbutamide 1 gm. daily because of a temporarily depleted hospital supply of the latter. His diet, digoxin and reserpine were continued. Fasting blood glucose on July 17 was 78 mg. per 100 ml. On July 22 and 23, the patient complained of intermittent "drowsiness."

On the morning of July 24, nine days after starting chlorpropamide, the patient could not be aroused. His arterial pressure was 160 mm. systolic, 100 mm. diastolic, pulse 70 and regular and respirations normal. A 50 per cent glucose solution was given intravenously and the patient rapidly responded. Blood glucose drawn prior to glucose administration was 57 mg. per 100 ml. Chlorpropamide was withheld and reserpine discontinued. During the day, the patient received, in addition to his usual diet, sweetened orange juice (960 cc. between 8 a.m. and 3 p.m., 400 cc. at 7 p.m., and 200 cc. at 9 p.m. with each 200 cc. representing approximately 25 gm. of carbohydrate, a supplement of 200 gm.). At 4 p.m. he complained of feeling drowsy; however, this sensation cleared with supper. No glycosuria was found during that day. At 10 p.m., he was found to be unresponsive and, on examination, was deeply comatose and in mild respiratory distress from excessive respiratory tract secretions. His pupils were dilated but reacted to light; his eyes showed purposeless movements and there was twitching of the left cheek. Vital signs were unchanged from previous examination. All muscles were markedly spastic with extremities exhibiting a "clasp-knife" effect. Deep tendon reflexes were hyperactive and positive Babinski signs were now present bilaterally. Fifty cubic centimeters of 50 per cent glucose in water produced clearing of the neurologic findings but the patient remained agitated, confused and drowsy. A second administration of intravenous 50 per cent glucose produced clearing of these symptoms. The blood glucose prior to glucose administration was 12 mg. per 100 ml. Glucose was given intravenously during the following six hours and the diet was continued. The patient received approximately 2400 calories, including 350 gm. of carbohydrate, during a twenty-four-hour period. On July 26, a double portion general diet estimated to contain 4000 calories, including 520 gm. of carbohydrate, was started. Fasting blood glucose on

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*All blood glucose determinations by the Somogyi-Nelson method.

TABLE 1

Summary of observations on patient following hospital admission

Date	Hypoglycemic agent	Blood glucose* (mg./100 ml.)	Carbohydrate intake (gm.)	Caloric intake (calories)	Mental status	Other drugs
7/14	Tolbutamide 1.0 gm. daily		180	1800 (diabetic diet)	Clear, depressed	Digoxin 0.5 mg. daily Reserpine 0.1 mg. 3 times daily
7/15	Chlorpropamide 0.5 gm. daily started	121	"	"	"	"
7/17		78	"	"	"	"
7/23	Last chlorpropamide taken 8 a.m.		"	"	Intermittent drowsiness	"
7/24 7 a.m.		57	25	100	First episode of coma, clearing with glucose	Reserpine discontinued
			180	1800		
			200	800		
4 p.m.					Drowsy	
10 p.m.		12	50	200	Second episode of coma, clearing with glucose	
7/25			100	400	Clear	
			180	1800		
			20	200		
7/26		77	520	4000 (double portion general diet)	"	
7/27		71	"	"	"	
7/28		90	"	"	"	

*All blood glucose done fasting or immediately prior to glucose administration.

July 26 and 27 was 77 and 71 mg. per 100 ml. respectively and ranged from 90 to 100 mg. over the next two weeks. An oral glucose tolerance test on August 10, while the patient was still on the above diet, showed a fasting blood glucose level of 97 mg. per 100 ml., a one-hour level of 206 mg., a two-hour level of 193 mg., and a three-hour level of 119 mg.

Persistent hypotension lasting for one week, with systolic pressures ranging from 80 to 100 mm., followed recovery from coma. Serial transaminase and electrocardiograms did not suggest recent myocardial damage. Electrolytes were within normal limits. In October 1959, urinalysis was unremarkable with a random specific gravity of 1.020; nonprotein nitrogen was 36 mg. per 100 ml. and an intravenous pyelogram, showing good concentration of dye bilaterally, was reported normal. The patient had recovered satisfactorily from his depression and his blood pressures had stabilized at levels of 110 to 120 mm. systolic. His diabetes had been controlled on an 1800-calorie diabetic diet alone.

DISCUSSION

Hypoglycemic reactions have been mentioned as complications in about 4 per cent of over 1,500 diabetic patients receiving a trial on chlorpropamide therapy.[1-6] Reactions on doses up to and including 1 gm. per day were primarily mild, characterized by such symptoms as hyperhydrosis, tremulousness, hunger, confusion and drowsiness, and responded rapidly to oral or intravenous glucose administration.

Hypoglycemic coma was rare, described in detail in only two patients.[8-9] In both cases, the reaction was neither profound nor recurrent. Another group[10] mentioned three severe hypoglycemic reactions but did not elaborate further. Care must be taken in attributing such symptoms as headache, light-headedness, vertigo, somnolence, weakness, ataxia, confusion and a variety of gastrointestinal disturbances to hypoglycemia, as these side effects have been observed in patients on chlorpropamide with normal or elevated blood sugar.[1-6]

Coates and Robbins[7] reported an eighty-eight-year-old diabetic female who developed severe, recurrent hypoglycemic shock, with a blood glucose level as low as 8 mg. per 100 ml., thirty-six hours after her last chlorpropamide ingestion, despite what was thought to

be adequate treatment. She had received 0.25 gm. of chlorpropamide daily for two weeks and 0.5 gm. on the day prior to the onset of her first reaction.

Our patient had tolerated tolbutamide in doses of 1 gm. daily for eight months and yet developed severe hypoglycemia on 0.5 gm. of chlorpropamide daily after nine days. At least part and perhaps all of this greater clinical potency is explained by slower rate of disappearance from the body.[11-12] Chlorpropamide, like other sulfonylureas, is excreted almost exclusively by the kidneys. This suggests that prolonged hypoglycemia might be related to impaired renal function; however, neither the present patient nor the previously reported case showed nitrogen retention. In addition, chlorpropamide, apparently unlike other sulfonylureas, is bound to serum protein to a variable degree. This may lead to a variation in excretion rate and/or tissue effect.[18]

During the first week of chlorpropamide therapy, there is a rapid cumulative increase in serum drug level.[14] Although Leevy and others[15] were able to demonstrate cumulative effect of chlorpropamide over a five-week period, Beaser[16] and Handelsman and others[17] showed that, on chronic administration, patients maintained blood chlorpropamide levels within narrow limits at a given oral dosage, showing no accumulation of drug.

The serum half life in vivo of a single dose of radioactive chlorpropamide is thirty-two to thirty-six hours, or about eight times that of tolbutamide and appreciable amounts are still circulating ninety-six hours after administration.[12-18] Carlozzi and others[14] studied daily serum chlorpropamide levels in normal men given chlorpropamide for fifteen days at doses of 0.25, 0.5, and 1.0 gm. daily. An interesting finding, most noticeable at the lower dosages, was that serum chlorpropamide levels often increased for forty-eight to seventy-two hours after discontinuing the drug. Only small amounts of chlorpropamide were excreted daily thereafter, so that significant levels still remained in the circulation two to three weeks after cessation of drug administration. These pharmacologic observations on accumulation and excretion of chlorpropamide help in the understanding of the events in the patient herein reported.

SUMMARY AND CONCLUSIONS

Severe hypoglycemic shock is reported in a fifty-five-year-old male with mild diabetes mellitus taking 0.5 gm. of chlorpropamide daily for nine days. Thirty-six hours after the last chlorpropamide ingestion, in spite of supplemental feedings, the patient developed his most severe reaction with a blood glucose of 12 mg. per 100 ml. This case emphasizes the need for careful observation of patients on chlorpropamide following its initiation. Hypoglycemic reactions, should they occur, must be treated with the knowledge that significant blood levels of chlorpropamide persist for days after discontinuance of the drug.

SUMMARIO IN INTERLINGUA

Sever Hypoglycemia Causate per Chlorpropamido

Es reportate un caso de sever choc hypoglycemic occurrente in un masculo de cinquanta-cinque annos de etate con leve diabete mellite qui habeva prendite 0,5 g de chlorpropamido per die durante un periodo de novem dies. Trenta-sex horas post le ultime ingestion de chlorpropamido, in despecto de alimentationes supplementari, le patiente disveloppava su plus sever reaction con un glucosa de sanguine de 12 mg per 100 ml. Iste caso servi a sublinear le necessitate de un cautissime observation de patientes sub tractamento a chlorpropamido post le initiation del curso de medication. Reactiones hypoglycemic—si tales occurre—debe esser tractate con le conoscimento que significative nivellos sanguinee de chlorpropamido persiste durante plure dies post le discontinuation del droga.

Depost le redaction del presente reporto, un altere caso de prolongate coma hypoglycemic resultante ab le ingestion de chlorpropamido ha essite reportate (Sackner, M. A., e Balian, L. J.: Sever Hypoglycemia post Ingestion de un Composito de Sulfonylurea. *Am. J. Med.* 28:135-42, 1960).

ADDENDUM

Since this report was written, another case of prolonged hypoglycemic coma resulting from chlorpropamide ingestion has been reported.[18]

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The 1960 Census of Population

The United States has a record of decennial censuses dating from 1790, when the Federal Marshals and their assistants, assigned the task of enumeration, came up with a count of 3,929,214. The 1960 census of population, taken as of April 1, is expected to turn up a total population of about 180,000,000. The count will be taken by 160,000 enumerators who, with their immediate crew leaders and supervisors, will receive a short, intensive training by the Bureau of the Census.

Each household will receive an Advance Census Report during the last week of March on which each member will be asked to list name, relationship to household head, sex, color or race, date of birth and marital status. This gives each member an opportunity to supply his own information. The enumerator who calls on or shortly after April 1 will transfer this information to a census schedule designed to facilitate mechanical processing toward final tabulations by means of newly designed electronic equipment. At every fourth household, the enumerator will leave a form asking for additional information, such as occupation, industry, place of birth, education, children ever borne, and migration. These forms will be mailed to a local census office. In the less densely settled areas, which include about one fifth of the population, the enumerator will record the additional information when he calls.

Although the primary purpose of the census of population is the reapportionment of representation in the House of Representatives, the results it produces are indispensable as guides for our economic and social functioning. They are used in apportioning funds by Federal and State government, planning urban development, projections of school and working populations and of the aged, market analysis, analysis of health and welfare problems, location of medical care facilities, and computation of birth and death rates. The decennial census of population is the only occasion which provides the basis for the detailed analysis of mortality by cause of death according to such characteristics as age, sex, race, marital status and place of residence.

Everybody benefits from the census of population, directly or indirectly, through the use of its results by government, by business, and by all engaged in health and welfare activity. Everyone should make sure that he is counted.

MORTIMER SPIEGELMAN
Associate Statistician, Metropolitan
Life Insurance Company

Birth Weight and Fetal Mortality in Pregnant Subdiabetic Rats

Arnold Lazarow, M.D., Ph.D., Jae Nam Kim, M.D., Ph.D., and Lemen J. Wells, Ph.D., Minneapolis

It has been reported that diabetic women frequently give histories of fetal overweight and of increased fetal mortality in pregnancies occurring many years before the development of manifest diabetes.[1] Wilkerson studied the glucose tolerance in a large series of pregnant women.[2] In those instances where he observed abnormal carbohydrate tolerance during pregnancy, he found that newborns weighing nine pounds or more occurred three times as frequently as in the group with normal carbohydrate tolerance.

Lazarow reported that subdiabetes in rats could be produced by injecting subthreshold doses of alloxan.[3] Although these rats had an abnormal tolerance to glucose, their fasting and postprandial blood sugars were normal. They did not show any glycosuria.

In two thirds of these animals, subdiabetes persisted for a period up to a year and more. One third of these animals developed manifest diabetes (hyperglycemia and glycosuria) during the first year.

The present study was undertaken to determine whether pregnant subdiabetic rats likewise show a high incidence of stillborns and overweight newborns.

METHODS

The animals used were albino rats of a subline of the Sprague-Dawley strain (Holtzman). Most of the rats were virgin females, 120 to 150 days in age, weighing between 230 and 280 gm. The rats were fed a standard diet of Purina fox chow. Food and water were supplied ad libitum. The experimental and control animals were maintained under similar conditions.

Production of subdiabetes: Alloxan was dissolved in distilled water to make a 2 or 4 per cent solution immediately prior to injection. Nonpregnant females were injected intravenously with alloxan in a dose of 25 or 30 mg. per kg. of body weight (Lazarow and Palay).[4] A few rats were injected with alloxan on the twelfth day of pregnancy. Those rats which did not show either hyperglycemia or glycosuria were subjected to glucose tolerance tests. Animals were fasted sixteen to eighteen hours and injected intravenously with a 30 per cent glucose solution in a dose of 3 gm. per kg. of body weight. Blood sugars (BS) were determined by the Folin-Malmros micromethod.[5] The diabetic index (I_D) which is a measure of the degree of abnormality of glucose tolerance was determined for each test, using the following formula (Coupland, Davidson and Lazarow).[6]

$$I_D = \frac{\text{1 hr. experimental BS}}{\text{1 hr. average normal BS}} \times \frac{\text{2 hr. experimental BS}}{\text{2 hr. average normal BS}}$$

In forty-two tolerance tests carried out in twelve normal rats, the average one- and two-hour blood sugar values were 175.2 and 111.9 mg. per cent, respectively, and those values were used in calculating the diabetic index. The index determined in normal rats equals 1.00 plus or minus the standard deviation of 0.30 (Coupland, Davidson, and Lazarow).[7]

All fourteen subdiabetic rats had diabetic indices greater than 2.0, i.e., more than three standard deviations greater than normal. In eleven of the rats used, subdiabetes was induced prior to pregnancy; in three, subdiabetes was induced on the twelfth day of pregnancy. Since the average birth weights and fetal mortalities were similar in the two subdiabetic groups, all of the subdiabetic rats were treated as a single group.

Blood sugar was determined at frequent intervals in all animals. The urine sugar was determined by the caramelization method of Somogyi.[8] The twenty-four-hour urinary excretion and the urine sugar level were determined at various times during the course of pregnancy, in order to be certain that none of the sub-

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diabetic rats developed manifest diabetes during the course of study.

Breeding: Vaginal smears were made daily in the experimental groups. An animal showing estrus was placed with males of the same strain and watched until copulation took place. Time of mating was recorded. After matings, females were caged separately.

Length of gestation: Beginning at twenty-one days and fifteen hours postcoitum, i.e., one hour prior to the earliest time of delivery in control pregnancies in this strain of rats (Wells),[9] the observations were made at intervals of fifteen to sixty minutes until spontaneous delivery. Thus, accurate observations on litter size and on stillborns could be made. Also, the length of gestation (time between witnessed mating and witnessed delivery of the first young) was accurate to less than one hour.

Weighing of newborns: Newborn rats were weighed individually immediately after birth and before the suckling of milk. In weighing a newborn, the chainomatic balance was read to the closest milligram.

RESULTS

The number of animals involved in each range of diabetic indices is given in table 1.

TABLE 1

Diabetic indices (I_D) of fourteen subdiabetic rats

Range of I_D	Number of animals*
2.00 to 2.50	7
2.51 to 3.00	2
3.01 to 3.50	2
3.51 to +	4

*One of the fourteen pregnant females produced two litters, hence is listed twice.

Birth weight: In analyzing the data, the average birth weight of a litter was used to calculate the standard deviations and the P values. Figure 1 shows that in the normal (control) group the mean birth weight of thirty-nine litters was 6.224 gm.; the standard error of the mean was 0.0815 gm. By contrast, in the subdiabetic group the mean birth weight of fifteen litters was 6.691 gm.; the standard error of the mean was 0.0918 gm. Thus, the mean birth weight of newborns born to subdiabetic mothers was 7.5 per cent greater than that of normal controls. This increase was statistically significant (P less than 0.001). There were no significant differences between the normal and subdiabetic groups in the length of gestation and in litter size.

When the birth weight of individual newborns was

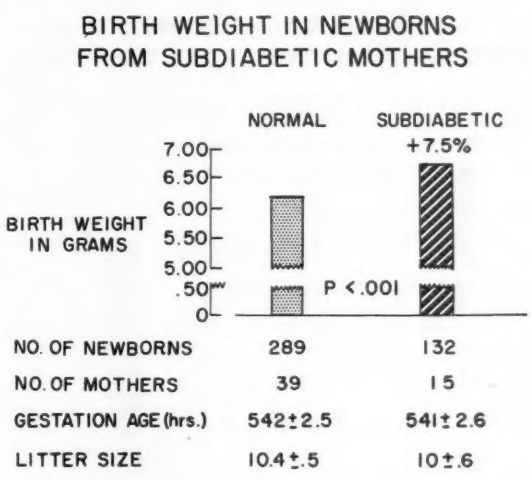

FIGURE 1

taken as an independent variable, the mean birth weight in 289 newborns from thirty-nine mothers was 6.274 gm. One standard deviation of the mean was 0.555 gm. Figure 2 shows the percentages of newborns whose weights exceeded the mean birth weight of the control group by 1, 2 and 3 standard deviations, respectively. In the normal control group, 14.2 per cent (forty-one out of 289 newborns) weighed 6.829 gm. or more (greater than one standard deviation from the mean); in the subdiabetic group, 30.3 per cent (forty out of 132 newborns) fell in the same range. The corresponding percentages for the normal and subdiabetic groups were 1 per cent and 3.8 per cent respectively at two standard deviations and 0 per cent and 1.5 per cent at three standard deviations. It should be noted that subdiabetic mothers produced overweight newborns 3.8 times more frequently than normal mothers (greater than two or more standard deviations). Furthermore, it is interesting to note that two out of 132 newborns from subdiabetic mothers weighed 7.939 gm. or more (more than three standard deviations greater than normal); whereas none of 289 newborns from normal mothers weighed that much.

Fetal mortality: In figure 3, the frequencies of stillbirths and neonatal deaths (newborns which had reflexes but which failed to breathe or survive) are recorded. The mortality in the normal group was 5.9 per cent (twenty-nine out of 289 newborns). By contrast, the mortality in the subdiabetic group was 18.7 per cent (twenty-eight out of 150 newborns). This increase in fetal mortality was statistically significant (P less than 0.001).

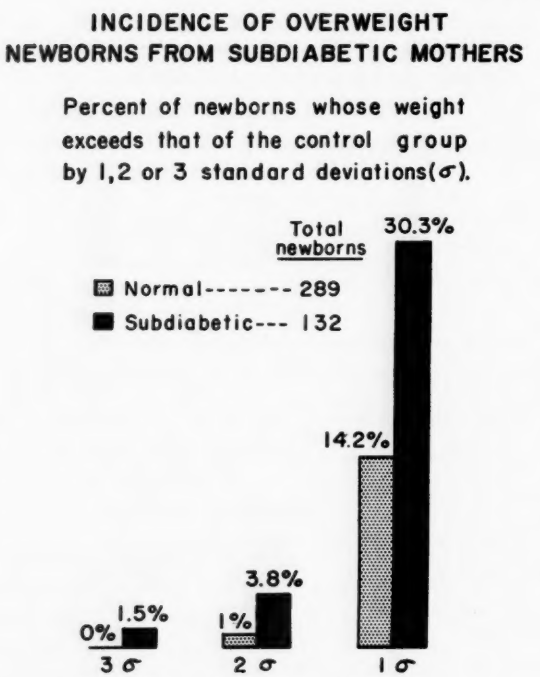

FIG. 2. The three weight limits at the bottom of the figure were calculated from the data on normal newborns (σ = standard deviation from the mean).

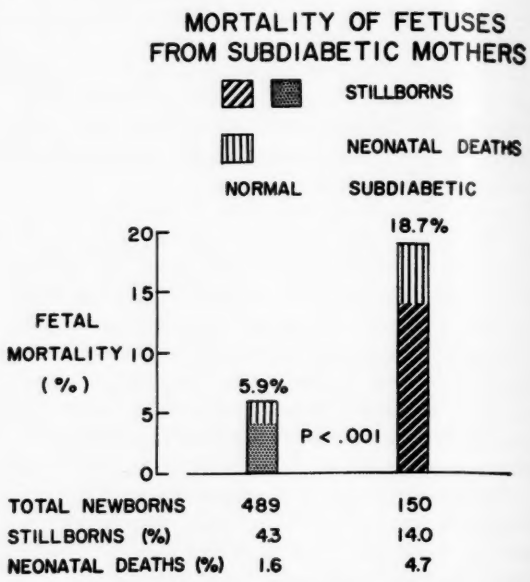

FIG. 3. Neonatal deaths are the deaths of newborns that had reflexes but failed to breathe and/or live one hour.

DISCUSSION

Overweight newborns (7.384 gm. or more) occurred about four times more frequently in newborns from subdiabetic mothers than in those from normal mothers. It should be noted that the increased birth weight in newborns from subdiabetic mothers occurred without any concomitant increase in the length of the gestation period. It has been reported that in the rat there is a positive correlation between the gestation age and the birth weight (Kim).[10]

In physical characteristics, although larger than those from control mothers, newborns from subdiabetic rats did not show evident signs of edema or of excessive fat accumulation. These findings suggest that subdiabetes stimulates the growth of fetuses in utero.

Miller, Hurwitz and Kuder,[1] defining an overweight human baby as one who weighs more than 5 kg., reported that the incidence of overweight babies born to prediabetic women is 3.9 per cent, whereas that in newborns from nondiabetic mothers is 0.07 per cent. Likewise, the average weight in infants born of prediabetic women was significantly greater than that in infants born of nondiabetic mothers. The increased birth weight and the increased fetal mortality were reported as early as one to three decades prior to the clinical onset of diabetes.[1,11,12]

Subdiabetic rats were apparently healthy, and did not excrete an excessive amount of urine. It should be noted that a significant increase in the incidence of stillbirths was observed in these subdiabetic rats at spontaneous delivery, even though their blood sugars were normal and they did not show glycosuria. It is of interest to point out that the mortality in the newborns from subdiabetic rats is similar to that reported for newborn infants from prediabetic women, i.e., 18.7 per cent and 14 per cent, respectively.[1] Similarly, the mortality rates for the normal rat and the normal human are 5.9 and 5 per cent, respectively (figure 3).[12]

Mechanisms which increase the fetal weight and fetal mortality are unknown. It is of interest to point out that the experimental induction of subdiabetes in the rat produces an increased fetal weight and increased fetal mortality. In the human, both maternal and paternal genetic factors are thought to contribute to fetal overweight.[12,13] If the mechanism by which subdiabetes in the rat produces increased fetal weight and fetal mortality can be determined, it may be possible to prevent these complications in the prediabetic human.

SUMMARY AND CONCLUSIONS

The effects of subdiabetes in the mother on fetal weight and fetal mortality were studied. Pregnancy in the subdiabetic rats was associated with a 7.5 per cent increased birth weight which was statistically significant —P less than 0.001; this occurs without any concomitant increase in the gestation period. The frequency of overweight newborns in the subdiabetic rats was severalfold greater than that in the normal rats. The fetal mortality in the subdiabetic group was three times greater than that in the normal controls—P less than 0.001.

SUMMARIO IN INTERLINGUA

Peso Natal e Mortalitate Fetal in Subdiabetic Rattos Pregnante

Esseva studiate le effecto de subdiabete in le ratta matre super le peso natal e le mortalitate fetal de su prole. Pregnantia in rattas subdiabetic esseva associate con un augmento de 7,5 pro cento in le peso natal. Isto es statisticamente significative—con un valor pro p de minus que 0,001. Il non occurre un concomitante extension del periodo gestatori. Le frequentia de neonatos a peso excessive ab rattas subdiabetic esseva plure vices plus grande que in rattas normal. Le mortalitate fetal in le gruppo de matres subdiabetic esseva tres vices plus alte que in le normal animales de controlo. Isto corresponde a un valor pro p de minus que 0,001.

ACKNOWLEDGMENT

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The arteriovenous differences in fasting subjects (*Nutrition Reviews 16*:102, 1958) indicated that the source of the circulating unesterified fatty acid was adipose tissue. Gordon and Cherkes calculated that if the adipose tissue were the primary source of the unesterified fatty acids, and if that tissue were to account for a significant fraction of the total metabolism of the rat, the adipose tissue should liberate approximately 100 micromoles of unesterified fatty acids per gram of tissue per hour. This rate is almost twenty times greater than that seen in any of their fasting rats (6.4 μM). They suggest that the low rate of unesterified fatty acid production in the in vitro experiments stems from the poor circulation, and that when the blood supply is intact the rate might be more nearly sufficient to account for the energy requirements. Although the amount of insulin incubated with the adipose tissue was at a concentration two orders of magnitude higher than that effective in vivo, they still felt their results suggested that insulin acted directly on the adipose tissue rather than some other tissue or organ.

Additional evidence suggesting that certain tissues liberate, while others utilize, unesterified fatty acids has been presented by P. S. Roheim and J. J. Spitzer (*Am. J. Physiol. 195*:288, 1958). They used sixteen normal dogs that had been fasted over night. In practically all cases there was a higher concentration of unesterified fatty acids in femoral vein blood than in femoral arterial blood. These differences ranged up to 0.49 μM. per liter, with most of them close to 0.15. The investigators interpreted this finding as indicating the release of lipids by the adipose tissue in the legs. There were no differences in the arterial and venous blood insofar as triglycerides, total and free cholesterol, or phospholipids were concerned.

From *Nutrition Reviews*, Vol. 17, No. 8, p. 242, August 1959.

Toxic Nephrosis in Rabbits Caused by the Hypoglycemic Biguanide, Phenformin

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The hypoglycemic biguanidine derivative, phenformin (DBI), has been shown to lower the blood sugar in various animal species[1] as well as in the diabetic human.[2-8] In contrast to the sulfonylureas which stimulate β cells,[9-13] the mechanism of action of this drug has not been clarified. Since it is effective in the alloxanized, the depancreatized and also the hepatectomized animal,[1,14] it has been suggested that the drug might exert a direct affect on cellular metabolism. In vitro experiments in high concentration have shown that it may act as an inhibitor of oxidative processes and that it promotes anaerobic glycolysis.[15-18] This action is similar to that of the early hypoglycemic guanidine preparation, Synthalin.[19,20] The clinical use of this latter drug was discontinued because of its toxic effect on liver and kidney.[21-27] On the other hand, phenformin up to the present has not been reported to cause pathologic changes in experimental animals[1] and in a report on three autopsied patients who had received this drug no specific histologic changes were observed.[28] However, others[29] have demonstrated in guinea pigs after four days that the drug may cause renal and hepatic damage. Similarly, in two rabbits treated intravenously for six days with large amounts of the drug, the authors found hyaline droplet formation and vacuolization of the proximal convoluted tubules of the kidney as well as a reduction in succinic dehydrogenase activity.[30] However, no changes in histochemically demonstrable glucose-6-phosphatase, alkaline or acid phosphatase, esterase, adenosine triphosphatase or 5-nucleotidase could be found.

The present study concerns the histologic alterations in liver, kidney, pancreas and muscle after prolonged administration of lower but still elevated dosages of the drug administered subcutaneously permitting survival of a large percentage of the animals up to six weeks. Furthermore, histochemical studies of intracellular oxidative enzymes in these tissues were undertaken in an attempt to elucidate the mechanism of the hypoglycemic action of the drug. As an indicator for anaerobic glycolysis, lactic dehydrogenase (LD) activity was utilized. Glucose-6-phosphate dehydrogenase (G-6-PD) activity was studied as an indicator for the pentose phosphate pathway and succinic dehydrogenase (SD) as an indicator for Krebs cycle activity.

From the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital and the Department of Pathology, Albert Einstein College of Medicine, New York, New York.

MATERIAL AND METHODS

The study was conducted on sixty-five New Zealand white rabbits weighing between 2 and 3.5 kg. Each animal received a subcutaneous injection of 25 mg./kg. of phenformin twice daily. Blood for glucose determination by the Nelson-Somogyi micromethod[31] was removed daily from the marginal ear vein. In addition blood for urea nitrogen determination was obtained biweekly. The surviving animals were sacrificed by overdosage with Nembutal at intervals from twenty-four hours to six weeks after starting therapy. Pancreas, kidney, liver and striated muscle were removed immediately and frozen in petroleum ether, kept at —70° by a bath of dry ice.[32] The frozen tissue was dried with filter paper and stored in stoppered tubes in the deep freeze at —20° C. Additional blocks of pancreas were placed in Zenker-formol solution and processed as previously described.[33] Sections were stained with hematoxylin and eosin as well as by the PAS trichrome method[34] with diastase control for glycogen identification, and also the aldehyde fuchsin method.[35] Additional blocks were embedded in carbowax and stained with Sudan IV for demonstration of neutral fat. G-6-PD, LD and SD activity were demonstrated as previously described.[34] An additional twelve rabbits served as uninjected controls.

RESULTS

Of the phenformin treated rabbits twenty-two (33.8 per cent) died spontaneously between the tenth and forty-second day after starting treatment. Tissues from these latter animals were not used for morphologic study. The morning blood sugar values in uninjected control rabbits ranged from 90 to 140 mg. per cent. During

treatment, the morning glycemic value varied between 71 and 160 mg. per cent. These latter values are not significantly different from those observed in untreated rabbits. The blood urea nitrogen of normal rabbits ranged up to 22 mg. per cent. In the phenformin treated animals there was an intermittent marked elevation of blood urea nitrogen with values ranging as high as 92 mg. per cent.

Regardless of duration of treatment with phenformin there were no definite histologic or histochemical alterations found in pancreas or skeletal muscle. Furthermore, no histologic changes were found in the liver except for one animal treated for four weeks in which areas of focal necrosis were seen. There were no definitely discernible changes in hepatic G-6-PD, LD or SD activity.

The kidney showed marked morphologic alterations which, however, did not occur uniformly in all treated animals. Some animals treated for long periods showed minimal lesions, whereas others after comparatively short times showed extensive changes. The earliest definite lesion appeared at five to eight days and consisted of vacuolization of epithelium of distal convoluted tubules and of the ascending limb of Henle's loop. The cytoplasm developed a foamy appearance due to varying sized vacuoles, while the nuclei were intact and centrally located (figure 1). In addition, hyaline droplets frequently appeared in the tubular epithelium. As treatment was prolonged a single vacuole filled the entire cell and the nuclei were frequently crescent-shaped and displaced to the periphery of the cell or had disappeared. The vacuoles contained neither Schiff positive nor sudanophilic material (figure 2). There was also increasing tubular dilatation and the lumina often contained dense Schiff positive material which resisted diastase digestion (figure 3). Untreated rabbit kidney occasionally showed similar lesions but these were very limited in distribution (figure 4).

With the progression of treatment the vacuolization became more extensive involving also the proximal convoluted tubules. By the third week these changes became accentuated and there was beginning replacement of renal parenchyma by fibrous tissue with infiltrates of lymphocytes, plasma cells and polynuclear leukocytes (figures 5, 6, 7). Eventually the number of vacuolated cells diminished but concomitantly there was progressively accentuated fibrosis so that by the sixth week there was marked diffuse and focal replacement of renal parenchyma by fibrous tissue. The residual tubuli were markedly dilated and frequently contained casts (figure 8). There was desquamation of epithelial lining cells and occasionally the tubular lumina contained foamy

FIG. 1. Rabbit kidney treated for five days with 25 mg./kg. of phenformin twice daily. There is foamy vacuolization of distal convoluted tubules, moderate dilatation and some cast formation. PAS Trichrome, X 250.

cells embedded in amorphous masses of diastase resistant PAS positive material (figure 9). Frequently the material within the tubular lumina became laminated and inspissated (figure 10). In addition, there appeared to be diminution in the number of glomeruli particularly in those cortical areas with the most extensive fibrosis. However, the remaining glomeruli showed no obvious alterations.

The three oxidative enzymes studied showed alterations which apparently follow the histologic changes. At early stages the normal small granular or rodlike cytoplasmic reactive structures for these enzymes became replaced by atypical large irregular granules. With increasing epithelial damage these disappeared and as could be expected, by the end of six weeks when there was replacement of parenchyma by fibrous tissue, large areas of the cortex showed loss of enzyme activity (figures 11 and 12).

DISCUSSION

Vacuolization and hyaline droplet formation in renal tubular epithelium was previously observed by the authors[30] in rabbits treated for six days with larger intravenous dosages of phenformin. However, the occa-

FIGURE 2

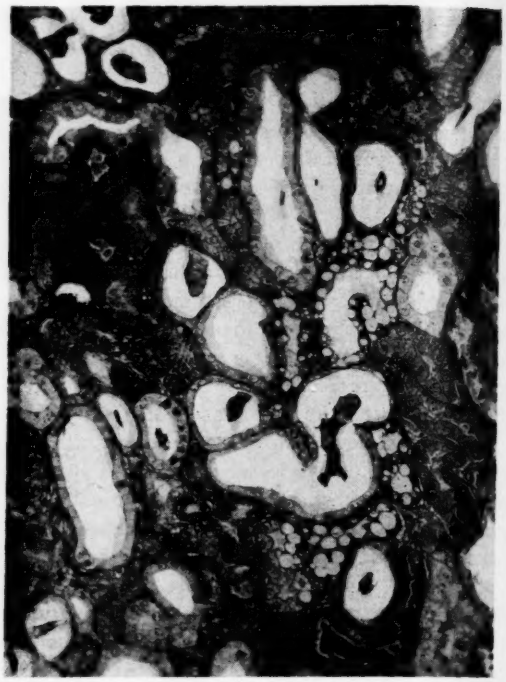

FIGURE 3

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FIGURE 4

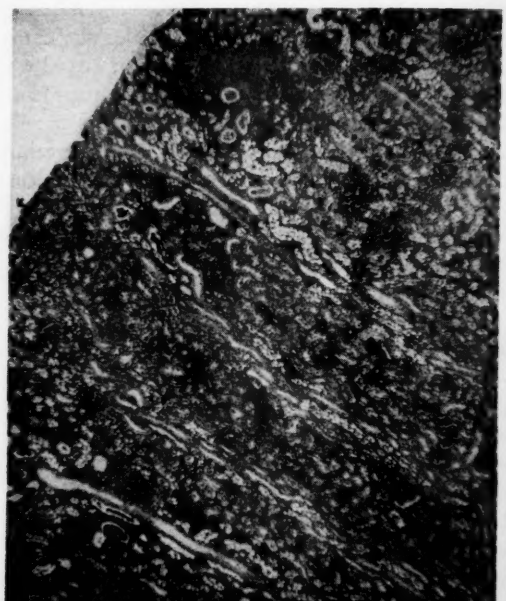

FIGURE 5

sional animals surviving more prolonged intravenous administration of smaller dosages of the drug did not show lesions comparable to those described in the present report. This discrepancy may be due to the fact that absorption of the drug from subcutaneous tissue is slower and the drug action would, therefore, extend for a greater part of the 24-hour period. In the present study, lower dosages of phenformin administered subcutaneously permitted survival of a larger percentage of the experimental animals. These animals develop renal lesions which become progressively accentuated with duration of treatment and eventually there is destruction of renal parenchyma with replacement fibrosis and infiltration by leukocytes. These results are at variance with those of others[1] who found no pathologic changes in guinea pigs or in a monkey after phenformin administration. On the other hand, some[28] have reported hepatic and renal damage in guinea pigs after phenformin. The renal lesion consisted of fatty degeneration and necrosis of tubular epithelium. The lesion in the rabbit differs in that no fat was found in the vacuolated epithelial cells and actual necrosis was not observed. Furthermore, no other workers to our knowledge have reported hyaline droplet formation in tubular epithelium. This phenomenon, which is indicative of cellular degeneration, is common to many forms of toxic nephrosis and is considered to result either from protein resorption from tubular lumina or from alteration of cytoplasmic constituents.

FIG. 2. Rabbit kidney treated for eleven days with 25 mg./kg. of phenformin twice daily. Many tubular epithelial cells are filled by single large vacuoles; others still have a foamy appearance. PAS Trichrome, X 375.

FIG. 3. Section of rabbit kidney treated with 25 mg./kg. of phenformin twice daily for two weeks. There is vacuolization of ductular epithelium as well as tubular dilatation with cast formation. PAS Trichrome, X 190.

FIG. 4. Normal rabbit kidney showing very occasional tubules with vacuolated epithelium. PAS Trichrome, X 65.

FIG. 5. Rabbit kidney treated for three weeks with 25 mg./kg. of phenformin twice daily. There is partial replacement of renal parenchyma by fibrous tissue with infiltrates of lymphocytes, plasma cells and occasional polynuclear cells. The rest of the parenchyma shows extensive tubular vacuolization. PAS Trichrome, X 50.

The hypoglycemic guanidine, Synthalin, has been shown to give toxic degenerative changes in the kidney.[21,23,26] The Synthalin-induced lesion differs, however, from that caused by phenformin and consists, in the rabbit, of severe necrosis of proximal convoluted tubules with ensuing uremia.[21] The renal changes found in the present study are similar rather to that which has been described after diethylene glycol ingestion.[26] This type of renal epithelial vacuolization appears to be completely different from lipid, sucrose or glycogenic vacuolizations which are reversible lesions. The irreversible destructive nature of the phenformin renal lesion is indicated by its progression paralleling the duration of treatment and the eventual extensive replacement of renal parenchyma by fibrous tissue.

The pathogenesis of the observed toxic nephrosis can only be hypothesized. It is probable, in view of the lack of destructive effect of the drug at other sites, that increased concentration in the renal tubular lumina is responsible or that it is resorbed by the renal epithelium and, therefore, attacks these cells. The enzymatic studies do not shed any additional light on the mechanism of renal parenchymal destruction. There was reduction of G-6-PD, LD and SD activity which, however, did not precede histologically observable damage to the cells. This signifies that these enzymes are not primary sites of action of the drug, but that they are affected only when cell integrity is disturbed. The failure to demonstrate changes in oxidative enzyme activity at sites other than the kidney is also in accord with this viewpoint. These findings do not throw additional light on the mechanism of the hypoglycemic action of phenformin.

Unlike other workers who found damage to pancreatic α cells[21,28] as well as changes in liver we found no such alterations in this study with the exception that one rabbit showed occasional areas of focal necrosis in the liver. However, in view of the fact that this hepatic lesion was found only in one animal, its relation to the drug administration is doubtful.

The question arises whether these observations in the rabbit are applicable to the human. The most prominent clinical symptom of phenformin administration is nausea.[3-5,7,8] No symptoms or findings related to renal damage have been reported. Furthermore, the so far limited number of autopsies reported do not indicate renal damage due to this drug. It is also possible that a human renal lesion after long-term phenformin administration might be masked by the nephropathy commonly found in the diabetic patient. It would, therefore, be important to differentiate between this renal lesion and any possible lesion due to long-term oral hypoglycemic therapy. The absence of renal findings in the human may be a question of species differences or of differences in dosage or route of administra-

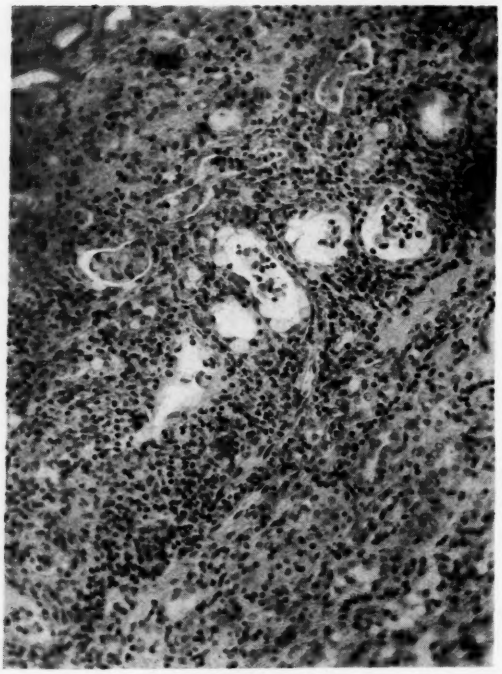

FIGURE 6

FIGURE 7

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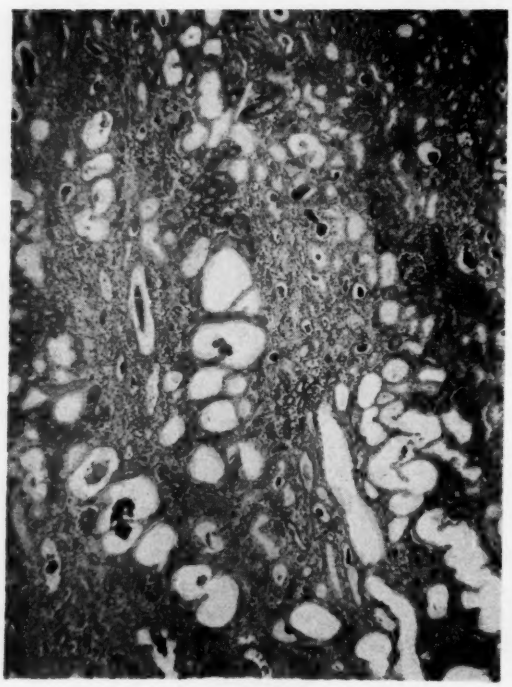

FIGURE 8

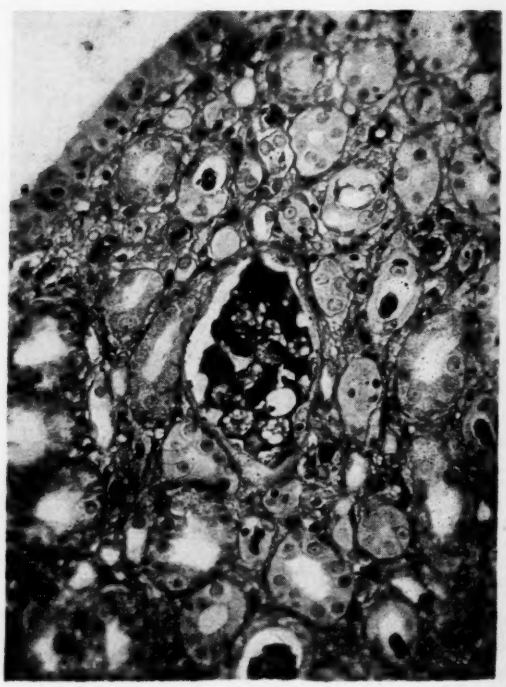

FIGURE 9

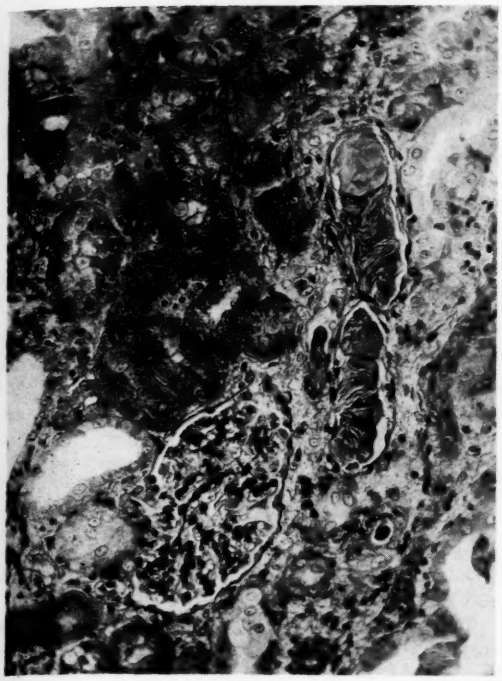

FIGURE 10

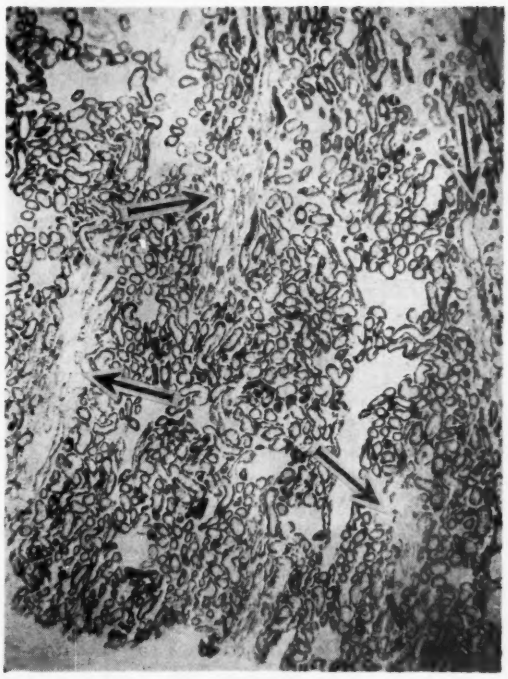

FIGURE 11

FIG. 6. High power view of same kidney as in figure 5, to show area of fibrosis with leukocytic infiltration. PAS Trichrome, X 190.

FIG. 7. High power view of same kidney as in figure 5, to show extensive ductular vacuolization in residual parenchyma. PAS Trichrome, X 190.

FIG. 8. Rabbit kidney treated for six weeks with 25 mg./kg. of phenformin twice daily. There is marked diffuse and focal replacement of renal parenchyma by fibrous tissue. The residual tubuli are dilated and frequently contain casts. PAS Trichrome, X 40.

FIG. 9. High power view of same kidney as in figure 8, to show cast composed of foamy cells embedded in amorphous PAS-positive diastase resistant material. PAS Trichrome-Diastase, X 250.

FIG. 10. High power view of same kidney as in figure 8, to show tubules with laminated inspissated casts of PAS-positive diastase resistant material. PAS Trichrome-Diastase, X 260.

FIG. 11. Rabbit kidney treated for three weeks with 25 mg./kg. of phenformin twice daily stained for succinic dehydrogenase. There is some diminution in activity with focal areas of almost complete disappearance (arrows). X 40.

FIG. 12. Rabbit kidney treated for six weeks with 25 mg./kg. of phenformin twice daily stained for succinic dehydrogenase. There is marked loss of activity with large areas which are almost completely unstained. X 40.

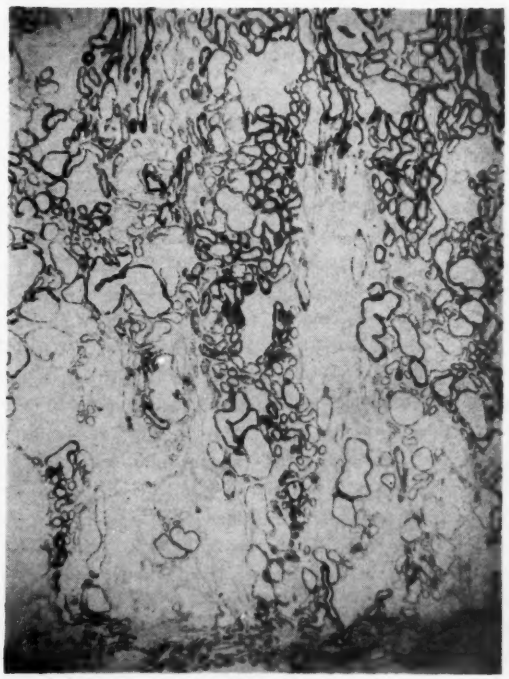

FIGURE 12

tion. For therapy of diabetes, up to 3 mg./kg. of the drug is administered orally in divided doses as compared with subcutaneous injection of 50 mg./kg. daily in two doses for the rabbits in these experiments.

SUMMARY

A histologic and histochemical study has been conducted of the effect on rabbit kidney, liver, pancreas and muscle of prolonged subcutaneous administration of 25 mg./kg. of phenformin twice daily. No definite alterations were found in pancreas, liver or muscle which were attributable to the drug. However, marked histologic changes were found in the kidney consisting of extensive vacuolization of tubular epithelium, tubular dilatation and cast formation and eventually fibrosis with loss of renal parenchyma. Early lesions were noted between the fifth and eighth day and were well advanced at two weeks. Fibrosis became evident after approximately three weeks of treatment, and, thereafter, became progressively more extensive. Histochemically demonstrable alterations of glucose-6-phosphate dehydrogenase, lactic dehydrogenase and succinic dehydrogenase activity followed the appearance of the histologic lesions in the tubules. The changes in these enzymes are therefore thought to reflect cellular damage rather than a primary site of action of the drug.

The observed toxic nephrosis is hypothesized to result from increased concentration of the phenformin in renal tubular lumina or to reflect resorption of the drug by renal epithelium.

SUMMARIO IN INTERLINGUA

Toxonephrosis in Conilios, Causate per le Biguanido Hypoglycemic, Phenformina

Esseva studiate histologia—e histochimicamente le effecto producite in ren, hepate, pancreas, e musculo de conilios per le prolongate administration subcutanee de 25 mg/kg de phenformina duo vices per die. Nulle definite alterationes esseva trovate in pancreas, hepate, o musculo. Tamen, marcate alterationes histologic esseva trovate in le ren. Istos consisteva de extense grados de vacuolisation del epithelio tubular, de dilatation tubular, e del formation de cylindros e, in le curso del tempore, de fibrosis con perdita de parenchyma renal. Precoce lesiones esseva notate inter le quinte e le octave die. Post duo septimanas le lesiones esseva ben avantiate. Fibrosis deveniva evidente post approximativemente tres septimanas de tractamento. Subsequentemente illo deveniva progressivemente plus extense. Le apparition del lesiones histologic in le tubulos esseva sequite per histochimicamente demonstrabile alterationes del activitate de dishydrogenase de glucosa-6-phosphato, de dishydrogenase lactic, e de dishydrogenase succinic. Le alterationes in le activitate de iste enzymas es consequentemente interpretate como un manifestation de injurias cellular plus tosto que un action primari del droga.

Es formulate le hypothese que le observate toxonephrosis resulta ab le augmentate concentration de phenformina in le tubulos renal o ab le resorption del droga per le epithelio renal.

ACKNOWLEDGMENT

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It appears that both statistical and physiological arguments can be advanced to suggest that when the body fat content of an individual of average body composition rises to the point where body weight increases 15 per cent above the median weight of healthy individuals age twenty-five, of the same height, he should be considered obese.

It is, of course, clear that the body weights of given individuals may give erroneous impressions about body composition because of differences in skeletal and muscular development, somatotype and hydration. Although the appraisal of body fat from body weight in individuals demonstrating only minor departures from average weight (within the 15 per cent of desired weight which we have considered normal) requires more sophisticated methodology than the scale, the diagnosis and rough appraisal of body fat content of the truly obese individual can be accomplished with simple methods. Four methods which are useful in appraising body fat content might be mentioned. These are (1) the visual method (the look); (2) the gravimetric method (the scale); (3) the digital method (skin-fold pinch); and (4) the aquatic method (body density and body water estimations). In the clinical diagnosis and treatment of obesity, information obtained by the first two is usually sufficient. Although it is unusual to have to depend upon more than the first three for clinical appraisal, the fourth method is useful in research.

From "Obesity as a Nutritional Disorder," by Robert E. Olson, in *Federation Proceedings*, Vol. 18, No. 2, Part II, pp. 59-60, July 1959.

The Effect of Tolbutamide on Toxic Liver Injury

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There is no conclusive evidence concerning the exact mode of action of oral hypoglycemic compounds. Although it seems to be established that some exert their effect only in the presence of insulin,[1] in our previous experiments it was shown that tolbutamide (N_1-tolylsulpho-N_2 butylcarbamid) inhibits the glycogenolytic effect of certain substances. Thyroxine (0.5 mg.), tubocurarine (30 gamma), and posterior pituitary extract (10 I.U.) were given simultaneously with tolbutamide. These drugs decrease the glycogen content of the liver, but differ in chemical structure and other characteristics. Since tolbutamide inhibited glycogenolysis due to these substances, we came to the conclusion that tolbutamide and other related drugs act—at least partly—by "defending" the glycogen content of the liver.[2]

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In further experiments we studied the postmortem disappearance of glycogen in rat liver slices. The autocatalytic decrease of glycogen can be considerably impeded by antemortem tolbutamide treatment of the intact animal in accordance with our previous hypothesis.[3]

The purpose of the present investigations was to find out whether experimental liver injury could be influenced by prior treatment with tolbutamide. Carbon tetrachloride poisoning seemed suitable for our purpose, since not only carbohydrate metabolism but excretory functions (bile secretion, bromsulphalein excretion) are also damaged, glutathione content of the liver diminishes, and inactivation of SH-groups can be observed.[4] Changes in carbohydrate metabolism were followed by determination of glycogen content; simultaneous histologic examination of the liver tissue showed the degree of cell damage. The injury thus demonstrated was com-

TABLE 1

0.25 ml. CCl_4 administered to each animal

Number of cases	With tolbutamide (50 mg. per day) Glycogen content of liver			Without tolbutamide (control cases) Glycogen content of liver		
	Determined by chemical method*	Estimated by stain method†	Degree of change in histologic pattern‡	Determined by chemical method*	Estimated by stain method†	Degree of change in histologic pattern‡
1.	0.9		++	0.7		++++
2.	2.5		+	0.6		++++
3.	1.2		++	0.5		++++
4.	1.3		++	0.6		++++
5.	1.3		+	0.3		+
6.	0.6		++	0.3		++
7.	0.4		+	0.9		++
8.	2.7		+	0.8		++
9.	0.4		++++	0.5		+
10.	0.3	++	++	0.2	+	++++
11.	0.3	+++	++	0.3	+	++++
12.	0.6	++++	+++	0.5	+++	++++
13.	0.8	+++	+++	0.3	+	++++
14.	0.7	++	+++	0.3	+	++
15.	0.6	++	+++	0.6	+	++
Mean	1.0			0.5		
Standard deviation	±0.74			±0.19		
	t 2.6					
	0.02>P>0.01					

* Glycogen gm./100 gm. liver.

† ++++ much +++ moderate ++ few + in traces.

‡ ++++ severe +++ diffuse ++ moderate + mild.

TABLE 2

0.125 ml. CCl_4 administered to each animal

Number of cases	With tolbutamide (50 mg. per day) Glycogen content of liver			Without tolbutamide (control cases) Glycogen content of liver		
	Determined by chemical method*	Estimated by stain method†	Degree of change in histologic pattern‡	Determined by chemical method*	Estimated by stain method†	Degree of change in histologic pattern‡
1.	0.7	+++	+++	0.3	++	+
2.	0.8	++++	+++	0.9	++++	++
3.	0.7	+++	+++	0.5	+	++
4.	0.8	+	++	0.4	++	++
5.	1.3	+++	+	0.2	+	+
6.	0.4	+++	+	0.3		+
7.	0.8	+	+	0.1		+
8.	1.0	++++	+	0.2		+
9.	1.2	++++	+	0.4		+
10.	1.0	++++	+	0.2		+
11.	1.1	+++	++	0.7	+++	++
12.	2.0	++++	++	0.7	++	++
13.	1.5	+++	++	0.5	+	++
14.	2.0	++++	++			
15.	3.4			1.3		
16.	3.0			1.1		
17.	2.1			1.6		
18.	2.9			1.1		
19.	2.3			0.8		
20.	2.2			0.6		
21.	2.5			0.6		
22.	2.6			0.9		
23.	2.2			0.2		
24.	1.9			1.0		
Mean	1.7			0.6		
Standard deviation	±0.85			±0.4		
		t 2.21 0.05>P>0.02				

* Glycogen gm./100 gm. liver.

† ++++ much +++ moderate ++ few + in traces.

‡ ++++ severe +++ diffuse ++ moderate + mild.

pared with the glycogen content of the cells estimated from histochemical stains on a scale of 1+ to 4+.

Experiments were performed on albino rats weighing 120 to 150 gm., kept on Sós diet containing 15 per cent protein, 6 to 8 per cent fat, vitamins, etc.[5] Fifteen rats were given 50 mg. tolbutamide (Rastinon-Hoechst) for five days in aqueous suspensions through a gastric tube. Another series of fifteen rats served as controls and were submitted to the same procedure but given physiologic saline. All thirty rats were given a single injection of carbon tetrachloride (0.25 ml.) on the third day. On the fifth day the rats were decapitated, glycogen determinations[6] and histologic procedures were begun immediately.

As the glycogen level of the livers was very small and histologic study revealed severe cell damage we repeated this experiment giving only 0.125 ml. carbon tetrachloride to another group of forty-seven rats. From this group twenty-three served as controls. Our results are presented in tables 1 and 2.

These indicate that glycogen levels are significantly higher in both groups treated with tolbutamide compared with the control group. Accordingly it may be assumed that the decrease of hepatic glycogen content following injections of carbon tetrachloride can be impeded by tolbutamide.

The degree of tissue damage and the glycogen content of the cells as seen by staining, arbitrarily graded, are shown in the tables. The pathologic alterations (hematoxylin-eosin and Sudan III hemalum) did not differ considerably in the two groups and consisted of diffuse centrilobular necrosis with inflammatory reactions around partly autolyzed cells. Extensive fatty degeneration was found around the necrotic zones. In the peripheral cells of the lobules only small fat droplets appeared. There was no substantial difference in respect

to necrosis or fatty degeneration between treated and control animals. The measure of cell injury apparently did not influence the glycogen content. But the intact hepatic cells in the treated groups contained histologically more glycogen (periodated leucofuchsin-hemalum, after Pearse), although the cell injury in general was very much alike. The chemical data and microscopic glycogen content were not always consistent. The explanation for this difference is that the glycogen content of the cells was estimated in the relatively intact peripheral cells and not in the injured cells. Thus the centrilobular area may not contain any glycogen, whereas peripherally there may be abundant storage of it.

Our results indicate that tolbutamide impedes the glycogenolysis even in diffuse "nonspecific" liver injury due to carbon tetrachloride. The decrease of hepatic glycogen is evidently just part of the diffuse metabolic damage. This complex injury could not be prevented by tolbutamide, just as we have no definitive proof of a beneficial effect in liver diseases.

SUMMARY

In carbon tetrachloride intoxication the hepatic glycogen level of rats treated prophylactically with tolbutamide is higher than in the controls.

There is no substantial difference in respect to necrosis or fatty degeneration in the two groups, but in the tolbutamide-treated animals more glycogen is demonstrable in histochemical preparations.

SUMMARIO IN INTERLINGUA

Le Effecto de Tolbutamido Super Injurias Toxic del Hepate

In intoxication per tetrachloruro de carbon le nivello hepatic de glycogeno in rattos prophylacticamente tractate con tolbutamido es plus alte que in rattos de controlo.

Esseva constatate nulle differentia substantial inter le duo gruppos con respecto a necrose o degeneration grasse, sed in le caso del animales tractate con tolbutamido plus glycogeno esseva demonstrabile in preparatos histochimic.

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On the average, the counterpressure of selection, consisting in the elimination of individuals with excess detrimental genes, almost exactly equals the pressure of mutation in producing these genes. There is evidence from more than one direction that in man at least one person in five, or 20 per cent, carries a detrimental gene which arose in the immediately preceding generation and that, therefore, this same proportion—one in five—is, typically, prevented by genetic defects from surviving to maturity or (if surviving) from reproducing. This equilibrium holds only when a population is living under conditions that have long prevailed. Modern technics are so efficacious that, used to the full, they might today (as judged by recent statistics on deaths and births) be able to save for life and for a virtually normal rate of reproduction some nine tenths of the otherwise genetically doomed 20 per cent. Assuming this to be the case, there would in the next generation be 18 per cent who carried along those defects that would have failed to be transmitted in the primitive or equilibrium population, plus another 20 per cent (partly overlapping the 18 per cent) who had the most recently arisen defects. At this rate, if the effectiveness of the technics did not diminish as their job grew, there would after about eight generations, or 240 years, be an accumulation of about 100 "genetic deaths" (scattered over many future generations) per 100 persons then living in addition to the regular "load of mutations" that any population would ordinarily carry. It can be estimated (on the supposition that human mutation rates are like those in mice) that this amount of increase in the load is about the same as would be brought about by an acute exposure of all the parents of one generation to 200r of gamma radiation, a situation similar to that at Hiroshima, or by a chronic, low-dose-rate exposure of each of the eight generations to 100r.

From "The Guidance of Human Evolution," by Herman J. Muller, Ph.D., D.Sc., in *Perspectives in Biology and Medicine*, Vol. III, No. 1, page 9, Autumn 1959, and in *Evolution after Darwin*, University of Chicago Press.

Diabetes and Work

A Study of the Place of Diabetics in the Labor Pattern

Elisa H. W. Wijnmalen, M.D., M.P.H., Leiden

Physicians caring for diabetics are faced with the problem of their capacity for work. The attitude that diabetes can incapacitate the individual for some kinds of work and often leads to physical disability is not unusual. This implies that the sickness absence of diabetics would be greater than that of nondiabetics. There is, however, little concrete information on this aspect of the subject. The literature contains only a few publications, most of them American,[1-5] dealing with the employment of the diabetic. The majority concentrate on special conditions of such employment, and a few illustrate the experience of companies with diabetic employees. In investigations of the latter type, results indicating that the work record of diabetics is satisfactory though in some cases slightly less favorable than that of nondiabetics were obtained by Brandaleone[3] (in a New York City bus company), Dublin and Marks[5] (in the New York City home office of the Metropolitan Life Insurance Company), MacConachy[6] (in the Philadelphia Electric Company), and by the U.S. Bureau of Labor Statistics[10] via a questionnaire sent to forty-five companies. The findings of these studies, however, pertain to a small number of diabetics.

In making any study of patients at work, either the disease or the work can serve as orientation factors. The former approach is simplified by the availability of the data collected by the attending physicians. Although this approach supplies a great deal of information concerning the nature of the work done by the diabetics, their education, and the problems they encounter in their work, it has the decisive drawback that these patients are scattered over such a large number of industries and companies that collecting a comparable control group without the disease but with the same working conditions is almost impossible.

Such difficulties can be avoided by taking the work as the starting point of the investigation and making up groups within comparable employment conditions. The diabetics can be located in concerns with available data on work and health, and these will be companies in which an occupational health service takes part in deciding the placement of employees and collects information about the state of health and incapacity for work of sick employees. Because in The Netherlands only the minority of the employed workers receive such care, it was impossible to reach the entire group of working diabetics, which in turn made it impossible to investigate a random sample of diabetics.

An evaluation of the place of the diabetic in the labor pattern must distinguish between those still to be employed and those who already have jobs, since the attitude toward a diabetic applying for work in a company differs from that toward a diabetic already employed. Two factors in the latter case are responsible for this difference: Firstly, a valuable employee already adjusted to the requirements of the job may be fitted into or kept in a type of work for which a diabetic applicant would not be chosen, and secondly, where the education and experience of an employee who has been with the company for some time exclude him from any other available position in the company, he may be kept as long as possible in his original job.

METHODS

Occupational health services of a number of companies served as the source of data for the investigation of the work of diabetic employees. Through a questionnaire the members of The Netherlands Society of Occupational Medicine were asked about the possibility of their companies' participation in the study.

The companies were selected on the basis of the size of their working force and the quality of their medical records. The number of employees per company had to be large enough to make investigation worth while. In actual practice this meant that because diabetes is relatively infrequent at the main working ages only the very largest concerns could be considered for the study. The quality of the records kept by the health services determined whether diabetic employees could be identified: A number of companies with a sufficiently large working force to make them eligible for study had to be excluded because of the disproportionate amount of time required to locate their diabetic employees.

From the Institute of Social Medicine of Leiden University, The Netherlands.

In these terms only three companies among all those originally considered proved suitable for a study of this nature. They were the three largest concerns in The Netherlands, the N. V. Philips' Gloeilampenfabrieken in Eindhoven, the entire mining industry in South Limburg, and the national Postal, Telegraph and Telephone Company (P.T.T.), and even these companies had such a small number of female diabetic employees that the investigation had to be limited to male diabetic employees.

For a study of this type it would be extremely useful to be able to express in concrete terms the value of an employee or a group of employees to a company. Unfortunately this can not be done in simple numerical figures, and various alternative methods such as analysis of sick absence, estimates made by an immediate supervisor or foreman, performance evaluation, etc., have been tried, but such methods reflect only one facet of the problem. In addition, in evaluating records it is essential to be able to tell whether sickness or some quite different factor was responsible for an unexpected change of work by a given employee.

It was originally intended that the present study cover sick absence for the period 1948 through 1956 at Philips and in the mining industry, and the years 1955 and 1956 at the P.T.T. At a later date it was extended to include the type of work done by the diabetics in 1955-1956 and the relation of these types of work to their expected careers in the company. Wherever possible the data on sick absence of diabetic employees are compared with those already compiled by the companies for the entire group of employees. Since the diabetic group comprises only 0.1 to 2 per cent (range according to age) of the total group and the control data were available only for the total group, the diabetic group has consequently been compared with the total group (i.e., including the diabetics). Data on the work performance of the diabetics were generally not comparable to those of the total group and have therefore primarily casuistic value.

The record system in use in each case determined the methods by which the diabetic employees of these companies were traced. Of the three methods used, each had its limitations but gave the greatest reliability for a given application, and in all cases selection as to sick absence or job problems was avoided. The data collected per individual concerned both the nature and duration of the diabetic condition, its severity, possible stabilization difficulties, information about other diseases, about the number, duration of and reason for sick absence, and the type of work done in and before 1955.

THE INVESTIGATION MADE AT THREE LARGE COMPANIES

An investigation to determine the work potential of diabetics was carried out in the three large companies mentioned previously. The size of the working force and the quality of the records of the occupational health services of these companies guaranteed within reasonable limits the possibility of studying their diabetic employees. The methods of investigation were adjusted to locally prevailing conditions.

The prevalence of diabetes in a given employee population depends on its age composition, the sex of the employees, the prevalence in the local population at large, the policy of selection for employment and, if detection is a routine practice, of the sensitivity of the method of detecting glycosuria. Of the three companies involved in this investigation, in one, early detection of diabetes was a regular procedure applied to all its wage earners; in another, only part of the total group was subjected to periodic health examinations including urinalysis, and in one company no detection program was carried out. The number of diabetics traced in this investigation also depended on the systems of documentation used by the individual occupational health services.

In the period 1948 through 1956 at the Philips' Gloeilampenfabrieken seventy-nine male diabetics were found in the group of wage earners with an approximate annual "prevalence" or proportion of five per 1,000; in the mining industry 123 male diabetics with an approximate annual "prevalence" of one to two per 1,000; and in the period 1955-1956 at the P.T.T. 262 male diabetics with an approximate annual "prevalence" of five per 1,000. For the investigation of working capacity there were available in 1955 data on 65, 103, and 262 employees of these concerns, respectively. This difference in figures is due to the fact that in 1955 some of the employees originally included in the investigation were no longer available. Two thirds of the diabetic groups investigated consisted of men of forty-five years and over, which is not surprising in view of the fact that diabetes is more frequent in older people. At Philips and in the mining industry, the largest number of diabetic employees was found in the forty-five to fifty-four-year age group, at the P.T.T., in the group which was fifty-five years and over. The "prevalence" by age group varied from less than one per 1,000 to twenty-six per 1,000.

The average total duration of employment was about twenty years, and duration after diagnosis of diabetes mellitus was about six years. In the mining industry, however, the duration of employment after diagnosis of

diabetes mellitus was shorter due to the frequency of retirement at ages below sixty-five. Of the total group of 464 diabetics, 436 developed the condition during employment by the company.

The severity of diabetes measured according to need for insulin treatment differed for the three companies. At Philips, one third of the diabetics were treated with insulin, in the mining industry two thirds, and at the P.T.T. one half. This reflected an inverse correlation with the number of diabetics found by way of early detection. Each of the companies had a few diabetic employees showing problems of stabilization, mostly of temporary nature.

A variety of chronic diseases was encountered among the diabetics, as could be expected in a group of this age composition. Cardiovascular diseases were found in about 20 per cent of the total group of diabetics. A surprising finding was that in the group of 123 mine workers only sixteen suffered from this type of disease but their average age was slightly lower than that of the diabetic group of Philips and P.T.T. Also common were diseases of the locomotor system, chronic bronchitis, stomach ulcers and gall bladder conditions. Special attention has been given to overweight. This condition was found in two fifths of the diabetic group, and there was more of it in the patients not receiving insulin than in the insulin-treated diabetics. Cardiovascular diseases were found in equal measure in these two groups of patients.

The group of 464 diabetics was too small and too heterogeneous for statistically valid conclusions; the findings of the sick absence study are therefore formulated in broad terms as follows:

1. At Philips and in the mining industry the percentage of persons with no absences in the diabetic group was identical with that of the control group. At the P.T.T. that of the diabetics was slightly lower. There are thus proportionally just as many nonabsentees among the diabetic employees as among the total group of employees.

2. The number of spells of sick absence during the observation period, related to the average number of persons under observation, was the same among the diabetic employees for all three companies as that of the total group, i.e., there is an equal number of spells of sick absence per man in both groups.

3. The length of absence, determined from the number of days absent, is in most cases greater for the diabetic group. This applies to the Philips group to only a limited extent; the mining industry and the P.T.T. groups show wider differences, although not of a nature to permit conclusion that the difference is important.

The proportional sick absence figures, which give a good picture of the proportion formed by the diabetic group in the sick absence total for the whole group, give a clear illustration of the findings just presented (tables 1 and 2).

Absence due to stabilization problems formed only a small proportion of the total sick absence of diabetics at Philips and the P.T.T. With the mining industry this was quite different, primarily because of two factors: the greater clinical severity of the mine workers' diabetes and the fact that for a number of these diabetics it was difficult to find suitable work on short notice (by suitability is meant regular, daytime duty without heavy physical exertion), with the result that they were absent more than would normally have been necessary in terms of their general state of health.

The investigation of working capacity concerned the types of work done by the diabetics in the period 1955-1956 and, where such information could be collected, the course of their careers in the company. Activities in the three companies naturally diverge considerably. The Philips factories are mainly concerned with the manufacture of electrical equipment; production of coal by the mining industry involves both underground and surface work; some of the work at the P.T.T. is administrative and some is physical work such as the mail-delivery service or technical services. The underground work and some of the surface work in the mining industry and the work of the mail-delivery service of the P.T.T. are considered to be heavy labor. At Philips and in the mining industry only blue collar and the lower level white collar jobs are represented, at the P.T.T. all functions.

In the Philips factories where heavy labor is exceptional, only three out of sixty-five diabetics were engaged in that type of work. For the mining industry this figure was fifty-five out of 103. Of the 262 diabetics working for the P.T.T. 148 did physical labor, eighty-one of them heavy and fifty-six medium-heavy. This means that in the mining industry and at the P.T.T. combined, 192 of the 251 diabetics who did physical labor were engaged in heavy or medium-heavy work. This finding is amazing considering the generally accepted policy of placing diabetics in nonheavy labor.

As far as information on shift work was available it was found that two of the sixty-five diabetics at Philips, fifty-four of 91* in the mines, and at least seventy (the

*The working hours of twelve of the 103 diabetics at the mines could not be traced at the time of the investigation.

TABLE 1

Proportional rates of sick absence of diabetic workers by industry and age groups

	Industry Age group	Diabetics Number	Diabetics Per 1,000 total employees	Ratio among diabetic employees to all employees x 1,000 Number of employees with sick absence	Number of spells of sick absence	Work time lost for sick absence
	Philips					
	under 45	10	1.4	2.0	1.6	2.2
1954	45 and over	40	11.6	10.4	8.9	10.2
	all ages	50	4.7	4.6	3.9	6.1
	under 45	14	1.9	2.5	3.3	6.9
1955	45 and over	43	12.1	10.4	10.5	11.7
	all ages	57	5.3	4.9	5.5	9.2
	Mining industry*					
	under 45	24	0.5	0.5	0.6	0.9
1956	45 and over	63	5.1	5.2	6.7	7.6
	all ages	87	1.6	1.5	1.5	2.9
	P.T.T.					
	under 45	53	1.7	1.9	2.0	2.4
1955	45 and over	202	14.2	13.5	13.7	22.2
	all ages	255	5.6	5.7	5.6	13.4

*Underground and surface workers combined

TABLE 2

Proportional rates of sick absence of diabetic workers in the mining industry for underground (U) or surface (S) work by age groups, 1956

Age group	Diabetics Number		Diabetics Per 1,000 employees		Ratio among diabetic employees to all employees x 1,000 Number of employees with sick absence*		Number of spells of sick absence		Work time lost for sick absence	
	U	S	U	S	U	S	U	S	U	S
under 45	12	12	0.5	0.7	—	—	0.6	0.7	0.8	1.2
45 and over	19	44	3.6	6.2	—	—	3.6	10.2	3.9	11.0
all ages	31	56	1.0	2.3	—	—	0.9	3.1	1.5	5.8

*Data separated as to underground and surface work were not available for the control group.

mail carriers) of 262 P.T.T. diabetics worked on either a two- or a three-shift system. The large number in the mining industry is particularly striking. It should be noted that twenty-eight of the fifty-four diabetics on a shift system in the mines were also in the group of fifty-five engaged in heavy labor.

Estimation by the supervisors, which is subjective and therefore limited in value, was used at Philips and the mines. Of 168 diabetics, forty-two were classed as very good, 115 as good, and eleven as adequate. In the cases where the work was graded as only adequate, no relation could be found between the mediocre performance and diabetes.

An attempt was made to determine the extent of the influence of diabetes on the employee's duties and career. This is no easy matter. Past situations could no longer be accounted for in all instances at the time of the investigation, although this occurred rarely. Often multiple rather than single circumstances are responsible for a change in a career. The worker's health is only one element in the picture, and diabetes is likely to be one of many factors involved, indeed may even be only the last straw. As well-supported an attempt as possible was made to evaluate the role of the diabetes in the picture, however, and working along these lines it can be said that in 70 per cent of the diabetic employees there was no change of work. This group did all types of work, some of it heavy, often in irregular shifts. In 11.5 per cent of the group, diabetes was the sole reason for change of work. In most cases the change concerned was from irregular shift-work to the same work in straight shifts; in some cases it meant change from heavy to lighter work, and in two cases it meant retirement with a disability pension. Five per cent of

the group required a change of work because of diabetes plus other reasons, mostly other diseases. In the remaining 13.5 per cent a change of work was effected because of other diseases and had no relation to the diabetes.

DISCUSSION

The present investigation has attempted to evaluate the diabetic employee against the background of the labor pattern as a whole. The positions and professions in which diabetics can be placed and those in which they are already represented are of course of interest in such a study, and attention was also given to the adjustment made by diabetics in their chosen work.

The use of the occupational health services as the source of the data for the study meant that the collected information concerned a selected group of employees. This method of investigation was nevertheless preferred because it was the only means available for making a comparative study of diabetics and nondiabetics.

The three large companies provided 464 diabetics for an extensive study of sick absence; in addition the type of work and work performance of 430 of these individuals were analyzed. The limited number and heterogeneity of the group made comparison with a control group unjustified, so that in the sick absence study differences were only considered significant if they were twice as great as the general experience. In such cases it is assumed that differences cannot in all probability be due to chance.

It should be noted here that in terms of present circumstances, no group of diabetic employees larger than the one described above could be found in The Netherlands for a comparative study of their place in the labor picture. The investigation of working capacity was limited to the diabetics.

The prevalence of diabetes in the employee populations found in this study is lower than in groups studied by others. In the study by Wade,[17] for example, not only the over-all prevalence but also the age-adjusted rates are higher than in the present study. A variety of circumstances are known to determine both prevalence and the number of diabetics actually found in this type of investigation. Whether in this case the prevalence among the population at large plays an important role is an open question.

The general conclusion concerning the sick absence of the 464 diabetics of these three concerns is that there are proportionally just as many nonabsentees among the diabetics as in the total group; that diabetics are responsible for proportionally as many spells of sick absence as the total group; and that they are absent relatively more days than the total group but not significantly so.

In the investigation of working capacity it was found that diabetics who perform nonheavy work during normal daytime working hours, in which risks resulting from a reduced level of consciousness are not encountered, constitute no special occupational health problem. Results of this study show further that a considerable number of diabetics are capable of medium-heavy and heavy work, even outside normal daytime shifts.

A few serious occupational-medical problems have appeared in relation to certain diabetics with stabilization difficulties. Here the attitude of the patient toward his diabetes was of great importance. In a number of cases of diabetes its combination with another disease incapacitated the patient and resulted in a change of work or retirement on pension.

At the conclusion of this intensive study of the largest group of diabetic employees available in The Netherlands for such an investigation, it is still not possible to generalize about the working capacities of the diabetic population. This negative conclusion is in itself of great significance, because the idea that there are important differences between diabetics and those who do not suffer from this disease is untenable on the basis of the results of this study.

The general propositions that diabetes is or is not an occupational health problem are both inaccurate. Each decision about the ability to work must be approached individually, and the judgment always based on the severity of the diabetes, the presence of other diseases, the attitude of the patient toward his physical condition, the nature of the work, and the circumstances under which the work must be performed.

SUMMARY

A total of 464 male diabetic employees of three large companies was studied to obtain information about (1) whether the diabetic is partially handicapped in performing work compared with the nondiabetic and (2) whether the diabetic has increased susceptibility to illness which might result in temporary or permanent disability. The preparatory investigation showed that only the three largest Dutch companies could supply a group of diabetics to compare with nondiabetics in the same work situation.

In these companies the differences in sick absence between male diabetic employees and their respective control groups were not of importance. Those in nonheavy work with normal daytime hours in types of

work where partial loss of consciousness due to hypoglycemia cannot constitute a danger, represent no special employment risk. A considerable number of the 464 diabetic employees were found to be doing heavy work and also work at other than normal daytime working hours.

SUMMARIO IN INTERLINGUA

Diabete e Travalio: Un Studio del Loco de Diabete in le Conjuncto del Travalio

Un total de 464 masculos diabetic, empleate per tres grande companias, esseva studiate pro obtener informationes relative al questiones de (1) si le diabetico es partialmente obstaculate in le effectuation de su travalio in comparation con le non-diabetico e (2) si le diabetico exhibi un augmentate susceptibilitate de contraher morbos, lo que poterea resultar in un invaliditate temporari o permanente. Un investigation preparatori habeva monstrate que solmente le tres plus grande companias hollandese poteva suppler un gruppo de diabeticos qui se prestava al comparation con non-diabeticos sub le mesme conditiones de travalio.

In iste companias le differentias in absentias causate per maladia inter empleatos mascule diabetic e le correspondente gruppos de controlo esseva disproviste de importantia. Subjectos ingagiate in travalio non-pesante, con normal horas diurne de occupation, in typos de activitate in que le perdita partial del conscietate in consequentia de hypoglycemia non constitue un periculo, non representa un risco special de empleo. Esseva trovate que un numero considerabile del 464 empleatos diabetic faceva travalio pesante o travaliava a tempores altere que le normal horas diurne.

ACKNOWLEDGMENT

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Obesity is not only an important nutritional problem in adults in this country, but also has become an important nutritional problem among school children. More than 10 per cent of the school children in two communities investigated were obese (*Nutrition Reviews* 15:6, 1957). Although long-term follow-up studies on the prognosis of obesity in childhood have not yet been carried out, a retrospective study of the role of juvenile obesity in adult obesity has recently appeared.

A. G. Mullins (*Arch. Dis. Child.* 33:307, 1958) recorded the age, sex, height and weight in 373 consecutive patients in a British medical outpatient department. One hundred and one of these patients were 20 per cent or more overweight when compared with the standard tables of W. F. F. Kemsley (*Ann. Eugen. Lond.* *16*:316, 1952).

Among these patients, those that had been known "fatty" at school (the most practical criterion) were classified as a juvenile obese group. The obese group included 26 per cent of the men and 44 per cent of the women. Approximately one third of the obese group were cases of persistent juvenile obesity and included five men and twenty-seven women. When the degree of obesity was classed as mild, moderate, or even severe depending on the relative per cent overweight, the juvenile obese group made up 53 per cent of those classified as severely obese, but only 12 per cent of those with mild obesity.

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Special Articles

Endocrine Factors in Lipid Mobilization

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It is generally agreed that adipose tissue is a dynamic "organ" capable of responding to a variety of stimuli. Endocrine factors influencing the release or accumulation of depot fat continue to be an intriguing and elusive subject of investigation. Extant knowledge about fat mobilization reviewed previously[1] has been supplemented by further observations which have not necessarily clarified the metabolic picture. The effect of caloric abundance or inadequacy upon the content of stored fat is well known. However, the mechanisms involved in fat deposition and release still are not completely understood. Newer information about the relationship of certain endocrine secretions to fat mobilization has again focused attention upon the influence of the pituitary-adrenal "axis" upon the flux of depot fat.

The pituitary gland was suspected early of having an effect on depot fat. It was reported[1] that when large doses of posterior pituitary extracts were injected into rats or rabbits, there resulted an accumulation of fat in the liver. An increase in liver fat and a decrease in carcass fat of the rat were observed three days after injection of beef anterior pituitary extract.[2] More recently Rudman and Seidman[3] found that the injection into rabbits of crude extracts of whole or anterior pituitary glands of hogs, sheep, cattle, or man, induced lipemia which was considerably greater than that induced by the purified anterior pituitary fractions. Thus it was suggested that the lipemia-producing substance might be an independent hormone, or that the lipemia was the result of synergistic action of known hormones. It is difficult to ascertain from this study whether or not the lipemia produced by the pituitary extracts, or the purified hormones, was mediated through another gland, such as the posterior pituitary, since the recipient animal was not hypophysectomized. The apparent similarity of action of posterior and anterior pituitary extracts on lipid mobilization needs further clarification.

Over the past five years cumulative reports have appeared from the Wyeth Institute for Medical Research providing evidence for the existence of a factor elaborated by the posterior pituitary gland and possessing marked mobilizing effects on depot fat.

In 1954 Seifter and Baeder[4] reported that the clearing effect of heparin was inhibited in vitro by addition of plasma from animals given cortisone, exposed to cold stress, or made nephrotic by the administration of anti-kidney serum. The term "clearing factor inhibitor" was given to this plasma substance. The activity of the inhibitor of the lipemia clearing factor remained after heating, suggesting that it was not a complex protein. The mechanism of its action was not known at the time. The same workers[5] later reported that "freeze-dried" dialysates of plasma from dogs, rats and horses receiving cortisone contained a lipid mobilizer (LM) which when injected into rats, mice, guinea pigs, rabbits, dogs, and humans markedly elevated plasma total fatty acids, total cholesterol and lipid phosphorus. The dialysate inhibited the "delactescing" action of heparin clearing factor, but its ability to mobilize depot fat was not dependent on this action. Similarly prepared dialysates from animals and human subjects not given cortisone were less active by a factor of 1,000. The inference was that cortisone injection stimulated release of LM from the pituitary, since cortisone injection failed to induce the appearance of LM in hypophysectomized animals. A single large injection of LM produced lipemia which persisted for over a week, and repeated large doses resulted in sustained hyperlipemia, hyperphagia, and in some instances weight loss and marked depletion of depot fat. LM was inactive when given orally. Further observations by the same group[6] resulted from an attempt to distinguish between LM and other lipemia producing agents. LM injection produced marked hyperlipemia in intact as well as hypophysectomized and adrenalectomized rats. In contrast, injection of protamine, di-isopropylfluorophosphate, and bacterial pyrogens failed to induce hyperlipemia in hypophysectomized rats suggesting that the production of hyperlipemia by these agents in intact rats was mediated through the adrenal-pituitary system. These results coupled with the observation that cortisone failed to release LM from hypophysectomized rats, led to consideration of the pos-

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terior pituitary gland as a possible site of LM elaboration. Thus the same investigators[7] prepared a dialysate from the posterior pituitary of hogs which proved to possess LM activity comparable to that previously reported for plasma dialysate from cortisone treated animals. Dialysate derived from 5 mg. of posterior pituitary tissue, when injected into intact, hypophysectomized or adrenalectomized rats, produced a twofold or greater increase in plasma total fatty acids, total cholesterol and lipid phosphorus. In contrast, injection of pitocin, pitressin, and anterior pituitary extract into hypophysectomized rats failed to induce any significant changes in plasma lipids. Further characterization of the LM material was reported from the same laboratory[8] when a crystalline polypeptide was isolated from plasma of horses treated with cortisone. The crystalline material possessed marked lipid mobilizing activity, with a minimal effective dose of 0.02 μg./kg. and without vasopressor or oxytocic actions. Further work on the chemical nature of this hormone-like substance appears to be in progress.

In any discussion of lipid mobilization, the role of the liver must always be a matter of concern. Administration of LM to hepatectomized rats resulted in hypertriglyceridemia without a corresponding elevation in plasma cholesterol or lipid phosphorus. This observation suggested that the source of the increased serum triglyceride was depot fat, and that the plasma elevation of cholesterol and lipid phosphorus in response to LM in nonhepatectomized rats may have been due to release of these substances from the liver in response to a triglyceride load. The ability of the liver to handle LM-induced hyperlipemia depended on the integrity and nutritional state of the liver. For example, it was possible to render the liver more "sensitive" to the hyperlipemic action of LM by previous administration of hepatotoxic agents. When given LM, the "sensitized" fasted rats could not readily dispose of the triglyceride mobilized from the depots, with resulting elevation in plasma of all lipid constituents. Simultaneous liver lipid analyses showed an increase in liver fat content, helping to support the conclusion that LM mobilizes triglycerides from depot fat.[9]

Such data from the Wyeth group provide further evidence for an endocrine control of lipid mobilization.[10] The sequence of metabolic events, during a catabolic process, is believed to be as follows: anterior pituitary secretion of ACTH, adrenal cortex and secretion of hydrocortisone, pituitary secretion of LM, mobilization of omental and mesenteric fat into the portal circulation.

The present method of assay for LM activity entails the demonstration of an increase in total fatty acid content of portal venous blood following LM injection into the recurrent saphenous vein of fasted rats.[11]

Certain experiments from other laboratories have lent support to the observations of Seifter et al. The presence of the pituitary has been found essential for the production of hyperlipemia of experimental nephrosis in rats.[12,13] Shotz and Page[14] have confirmed the observation that hypophysectomy abolishes protamine-induced hyperlipemia. A polypeptide with lipid mobilizing properties has been isolated from human urine.[15] An inhibitor of the in vitro clearing factor has been found in normal bovine plasma,[16] and in the plasma of patients with familial hyperlipemia,[17] following cortisone administration,[18] following injection of toxic doses of alloxan in rats,[19] and after repeated bleeding in rabbits.[20] In the latter instance heparin failed to influence the degree of lipemia produced by repeated bleeding. It is well to emphasize that the degree of clearing factor inhibition in vitro has not been equated by Seifter and associates with in vivo inhibition, nor does the latter activity determine the hyperlipemia attributable to LM.

Preliminary studies with LM in man have been done. Steiger et al.[21] reported a marked rise in plasma total fatty acids and serum lipid phosphorus and cholesterol in twenty-five human subjects following a single injection (1.0 mg./kg.) of plasma dialysate containing LM activity. Plasma lipid values reached their maximum two to three hours after the single injection and remained elevated for at least twenty-four hours. In addition, sustained hyperlipemia was induced in two patients who were given daily injections of LM for five and fourteen days. No toxic effects occurred that were attributable to LM. Further studies with LM in man[22,23] indicated that prefeeding modified the individual's response to LM. Daily intravenous administration of LM for two weeks to subjects previously maintained on a low fat diet (4.8 gm. per day of fat) resulted in a striking elevation of plasma lipids, sustained throughout the period of injection, and falling off to pre-injection levels within one to two weeks following cessation of LM treatment. In contrast, subjects maintained on a high fat diet (153 gm.) did not exhibit a hyperlipemic response to LM. Test meals of glucose or cream in acute experiments abolished the effect of a single injection of LM. No such blockade of the hyperlipemic effect of LM occurred when the subjects were given an amino acid mixture as the test meal. The interpretation of the result with glucose was that glucose administration somehow helped the liver to handle the triglyceride load brought about by LM. The inhibitory effect of prefeeding with fat re-

mained unexplained. It is of interest that in some of these studies crystalline LM was used, and this preparation was effective in as small a dose as 0.02 μg./kg. of body weight. More recently Zarafonetis et al.[24] demonstrated increased LM activity in twenty-six patients undergoing surgical stress. A significant shift from α to β lipoprotein as measured by paper electrophoresis of omental vein blood during surgery was observed. Moreover, cholesterol and lipid phosphorus levels were higher in the omental artery than they were in the omental vein, suggesting liver mobilization of these lipids or possibly removal of the lipids by the omentum. Existence of increased LM activity during surgery was suggested by three observations: (1) rise in omental vein triglycerides; (2) ability of the patient's plasma, obtained during surgery, to inhibit the delactescing action of heparin; and (3) LM activity of a dialysate of such plasma when injected into fasted rats.

Many of the factors influencing lipemia clearing have escaped elucidation. As mentioned earlier, heparin (a sulfated mucopolysaccharide) appears to clear alimentary lipemia through activation of a clearing factor (lipoprotein lipase). In contrast, the mobilization lipemia occurring in response to LM was not cleared by heparin. Moreover, a nonsulfated mucopolysaccharide, partially depolymerized hyaluronic acid (PDHA), a substance devoid of fat splitting activity, when injected or when given orally, was able to abolish the lipemia produced by LM. The inability of PDHA to split fat, and the continued detection of LM activity despite the lipemia clearing, suggested that PDHA produced clearing of lipemia by antagonizing the action of LM on depot fat.[25] The use of PDHA in the treatment of patients with lipemias having demonstrable LM activity, such as familial hyperlipemia, has been encouraging in a limited number of patients.[25] PDHA was shown to inhibit lipid mobilization in response to surgical stress.[26]

There have been no reports on the influence of LM on plasma nonesterified fatty acids (NEFA) whose release from depot fat constitutes one index of fat mobilization. The regulation of NEFA release is apparently dependent in part on the availability of glucose for oxidation.[27] It has not been determined whether LM plays any role in the pathogenesis of lipemia frequently seen in diabetes mellitus. Knobil[28] has shown, in rats, that administration of growth hormone stimulates and hypophysectomy inhibits NEFA release, in vitro, from epididymal fat tissue. There was no mention in this study whether or not the hypophysectomy was complete or whether there was any release of triglyceride into the incubating medium. The relationship of growth hormone to the LM system is unknown, nor is it known whether NEFA release from adipose tissue is independent of triglyceride release.

In any case, further evidence has been obtained of the responsiveness to hormonal influences of adipose tissue. The studies of Seifter and associates suggest that a hormone-like material (LM) is elaborated or stored in the posterior pituitary. This substance has a potent mobilizing effect on omental and mesenteric fat. The mobilized triglycerides reach the liver, which may store or metabolize the fat, or permit it to be released into the peripheral circulation. Various agents such as protamine and stressful events such as surgery are believed to induce lipemia by stimulating LM release. The action of LM on depot fat apparently can be inhibited by a nonsulfated partially depolymerized hyaluronic acid. It is worth noting that the interesting observations on LM all have been reported by one group of workers. Thus, confirmatory studies by other investigators are badly needed. It is conceivable that the pituitary gland elaborates more than one hormone concerned with fat mobilization; thus, the results obtained with anterior pituitary extracts on the one hand and with posterior pituitary preparations on the other are not necessarily mutually incompatible.

In view of the importance of the subject in the scheme of knowledge about metabolism, it is surprising that work on the endocrine control of fat mobilization has lagged until recently. Conceivably, the isolation of a hormone specifically concerned with lipid mobilization will provide the physician with a valuable adjunct in the treatment of obesity. Further light also may be shed on the various clinical hyperlipemias. Physiologists and clinicians alike will await further news about the phenomena of lipid mobilization with great interest.

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One of the recent significant developments in the field of lipid metabolism is the recognition that unesterified fatty acids in the blood play a biologically important role (*Nutrition Reviews* 16:102, 135, 1958). V. P. Dole and his associates and R. S. Gordon, Jr., and his associates verified the earlier finding of Szent-Gyorgy and Tominaga (*Biochem. Zeit.* 146:226, 1924) that blood normally contains a small amount of unesterified fatty acids.

The more recent workers have gone on to demonstrate that these fatty acids contribute significantly to the total metabolism of both man and animals. The level of these fatty acids in the blood fluctuates in an inverse relation to the level of carbohydrate metabolism. Those factors which enhance the rate of carbohydrate metabolism, reduce the level of unesterified fatty acids in the blood.

The previous work of Gordon and associates suggested very strongly that the adipose tissue is a source of the blood unesterified fatty acids. R. S. Gordon, Jr., and A. Cherkes (*Proc. Soc. Exp. Biol. & Med.* 97:150, 1958) studied the effect of insulin on the in vitro liberation of unesterified fatty acids from adipose tissue.

Their studies indicated that the nutritional state of the animal had a pronounced effect upon the in vitro liberation of unesterified fatty acids by the epididymal fat pad. The rate of production was markedly reduced when the rats were given a 10 per cent glucose solution for the eighteen hours prior to sacrifice when compared with the rats that had been starved (0.2 versus 6.4 μM unesterified fatty acids per gram of tissue per hour, respectively).

In similar experiments with rats that had been starved for eighteen hours, the adipose tissue that was incubated with insulin produced less unesterified fatty acids than the contralateral control tissue (—1.0 versus +1.6 μM per gram of tissue per hour, respectively).

These workers stated that the liberation of unesterified fatty acids from the adipose tissue in experiments in vitro supported their earlier conclusion. Their thesis is that those factors that enhance carbohydrate utilization (e.g., insulin) reduce the liberation of unesterified fatty acids, while those that increase the requirement for calories (e.g., starvation) increase it.

From *Nutrition Reviews*, Vol. 17, No. 8, pp. 241, 242, August 1959.

Recent Statistics on Diabetes

From present indications, in the year 1959 there was registered a slight increase in the recorded death rate from diabetes in the United States as compared with the previous year. For the first nine months of 1959, the provisional death rate based upon the 10 per cent sample of death certificates was 16.0 per 100,000 as against 15.6 in the corresponding period of 1958. No special significance can be attached to this difference, although it may be noted that it has occurred in a period of relatively good general health conditions. The provisional death rates from all causes of death and from the major cardiovascular-renal diseases during the first nine months of 1959 showed a small decline from the corresponding months of 1958.

Preliminary data on mortality from diabetes among the insured urban population represented by the Industrial policyholders of the Metropolitan Life Insurance Company show a trend opposite to that for the country as a whole. During the first nine months of 1959, the death rate from diabetes in that experience showed a modest decline, and this applies to the year as a whole, with a death rate of 14.7 per 100,000 in 1959 as compared with 15.2 in 1958.

Paralleling the trend among insured policyholders are the trends generally in the Eastern Seaboard areas for which data are regularly obtained as shown in table 1. In the two large Canadian cities, Toronto and Montreal, the mortality from diabetes shows opposite trends between 1958 and 1959. The provisional rate for Toronto registered a sharp decline, whereas for Montreal the rate rose appreciably. In England a modest decline was recorded for London Administrative County for the first nine months of 1959 from 1958. In the country as a whole during the first half of the year the rate was less than in 1958. This decline, however, was limited to females, the rate for males being identical for two years.

Regional data for the United States, based upon the 10 per cent sample as shown in table 2, show no consistent trend. The rates in the first nine months of 1959 are notably higher than in the corresponding period of 1958 in the Middle Atlantic and West North Central regions, but appreciably lower in the South Atlantic and East South Central regions.

TABLE 1

Recent data on diabetes mortality
Deaths and death rates—January-September 1959 and 1958

Area	Death rates per 100,000		Number of deaths	
	1959	1958	1959	1958
United States (10 per cent sample)	16.0	15.6	2,101	2,010
Metropolitan Life Insurance Company Industrial policyholders	15.1	15.7	1,845	1,995
New York State	18.2	18.7	2,287	2,324
New York City	19.1	20.5	1,153	1,235
Maryland	17.7	17.1	405	382
Baltimore	23.3	24.9	172	181
Boston	16.6	18.6	90	98
Philadelphia, resident	20.0	20.5	329	338
Toronto	16.8	20.5	83	101
Montreal, resident	15.8	13.7	138	118
London (Administrative County)	7.6	8.1	183	197
	Jan.-June		Jan.-June	
England and Wales				
Total	7.5	7.8	1,708	1,758
Males	5.5	5.5	606	602
Females	9.4	9.9	1,102	1,156

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in "Current Mortality Analysis," a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

Provisional data for the whole year 1958 show a drop from the rate recorded in 1957. As table 3 shows, this decrease reflects largely the trend at ages under sixty-five. Only at ages eighty-five and over was there a substantial increase in the death rate.

Analysis of the provisional data by race and sex for all ages combined shows that most of the decline between the two years occurred among females. The rates for males show little change (table 4).

Final data on diabetes mortality in the population of the United States are now available for the year 1957 and are shown in table 5, in detail by age, race and sex.*

Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual materials suitable for this section in future issues from Association members and other readers of the Journal.

*Figures by quinquennial age groups are available from "Mortality from Selected Causes, By Age, Race and Sex: United States, 1957," *Vital Statistics—Special Reports*, Vol. 50, No. 5, April 24, 1959.

TABLE 2

Number of deaths and death rates from diabetes in geographic division: United States reporting area for the 10 per cent sample; January-September 1959, 1958 and 1957

Geographic division	Death rates per 100,000*			Number of deaths*		
	1959	1958	1957	1959	1958	1957
U. S. reporting area	16.0	15.6	15.9	2,101	2,010	2,019
New England	19.4	20.3	21.1	141	139	155
Middle Atlantic	22.2	19.5	20.3	553	483	498
East North Central	18.1	19.1	18.0	494	508	470
West North Central	17.1	14.7	16.7	199	169	189
South Atlantic	11.8	13.3	13.5	228	251	249
East South Central	11.7	13.1	10.3	106	117	91
West South Central	13.6	12.6	12.7	171	156	155
Mountain	9.7	8.7	11.2	49	42	53
Pacific	11.4	10.3	11.6	160	145	159

*Excludes armed forces overseas.

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3

Deaths and death rates from diabetes by age. United States, 1958 and 1957

Age period (year)	Death rates per 100,000		Number of deaths	
	1958	1957	1958*	1957
Total	15.4	16.0	26,670	27,180
Under 1	—	0.3	—	12
1-14	0.4	0.4	180	188
15-24	0.7	1.1	160	253
25-34	2.1	2.6	480	620
35-44	2.9	4.6	690	1,064
45-54	9.5	11.1	1,910	2,182
55-64	37.1	38.0	5,620	5,684
65-74	97.7	97.8	9,640	9,526
75-84	148.7	151.2	6,440	6,324
85+	180.7	157.9	1,520	1,314
Not stated			30	13

*Estimated from 10 per cent sample. Classified by the Seventh Revision.

Note: Includes deaths only occurring within the continental United States.

Source: National Office of Vital Statistics—For 1958, Monthly Vital Statistics Report, Annual Summary, Part 2. For 1957, Vital Statistics—Special Reports, National Summaries, Vol. 50, No. 5, April 24, 1959.

TABLE 4

Deaths and death rates from diabetes by race and sex. United States, 1958 and 1957

Race and sex	Death rates per 100,000		Number of deaths	
	1958	1957	1958*	1957
All races				
Total	15.4	16.0	26,670	27,180
Male	12.5	12.6	10,680	10,605
Female	18.2	19.2	15,990	16,575
White				
Total	15.4	16.0	23,770	24,234
Male	12.7	12.9	9,650	9,623
Female	18.1	19.0	14,120	14,611
Nonwhite				
Total	15.1	15.7	2,900	2,946
Male	11.0	10.8	1,030	982
Female	19.0	20.4	1,870	1,964

*Estimated from 10 per cent sample. Classified by the Seventh Revision.

Note: Includes deaths only occurring within the continental United States.

Source: National Office of Vital Statistics—For 1958, Monthly Vital Statistics Report, Annual Summary, Part 2. For 1957, Vital Statistics—Special Reports, National Summaries, Vol. 50, No. 5, April 24, 1959.

At all ages combined, both crude and age-adjusted rates are given. The figures show the characteristic excess in female mortality from diabetes over that of males among both whites and nonwhites. This is due in part to the higher proportions of females at the older ages. Consequently, the difference between the two sexes is appreciably less for the age-adjusted rates than for the crude rates. In like manner comparative levels of diabetes mortality among white and nonwhite males and between white and nonwhite females differ as between crude and age-adjusted rates, the latter showing an excess of 20 per cent for nonwhite over white males and an excess of more than 70 per cent for nonwhite females over white females.

Among white persons, the female rates are generally higher than for males at ages under twenty-five, lower at ages twenty-five to fifty-four and higher again at ages fifty-five and over. The excess is greatest at ages sixty-

TABLE 5

Death rates per 100,000 from diabetes mellitus by age, color and sex. United States, 1957

Age	Total			White			Nonwhite		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
All Ages									
Crude	16.0	12.6	19.2	16.0	12.9	19.0	15.7	10.8	20.4
Adjusted*	13.5	11.3	15.4	12.9	11.1	14.5	19.3	13.3	24.9
Under 1	0.3	0.2	0.5	0.2	0.1	0.4	0.7	0.4	1.1
1-4	0.3	0.3	0.3	0.3	0.3	0.2	0.3	0.2	0.4
5-14	0.4	0.3	0.5	0.4	0.3	0.5	0.6	0.4	0.7
15-24	1.1	1.0	1.3	1.0	0.9	1.2	2.0	1.9	2.0
25-34	2.6	3.0	2.3	2.5	2.8	2.1	4.0	4.4	3.5
35-44	4.6	5.0	4.1	3.9	4.7	3.1	10.9	8.0	13.5
45-54	11.1	10.3	11.8	9.2	9.6	8.8	29.1	17.1	40.2
55-64	38.0	29.5	46.1	35.3	28.6	41.6	68.5	39.4	96.6
65-74	97.8	76.0	117.2	96.4	75.0	115.4	117.9	90.4	144.7
75-84	151.2	129.8	168.0	154.8	134.3	170.8	101.8	73.1	127.5
85+	157.9	140.5	170.5	167.6	148.6	181.1	71.1	75.0	69.6

*Based on age distribution of the total population of the United States in 1940.
Source: National Office of Vital Statistics—Vital Statistics of the United States, 1957, Vol. 1.
Note: Includes deaths only occurring within the continental United States.

five to seventy-four. Among nonwhites the female rates are the higher through the greater part of the life span and the excess is particularly marked at forty-five to sixty-four when the female death rate is more than double that for males. Among nonwhites of both sexes the recorded rates reach a maximum at ages sixty-five to seventy-four. At ages seventy-five and over, rates for nonwhites are well below those for whites. This may reflect the frequency of undiscovered diabetes in elderly Negroes.

Table 6 gives data on comparability ratios for diabetes and for certain other major causes based upon deaths classified according to the *Seventh Revision of the International List of Causes of Death* as compared with the *Sixth Revision.* This table is similar to that presented a year ago (DIABETES, March-April 1959, p. 153), but is based on the data for the 10 per cent sample of death certificates for the whole year 1958. The comparability ratio for diabetes is 1.01, or slightly less than that previously shown for the first six months of the year. Eventually, further data on this matter will be available by age.

TABLE 6

Provisional comparability ratios for certain causes. United States, 1958

Cause of death (Seventh Revision of the International Lists, 1955)	Ratio*
Diabetes mellitus	1.01
Malignant neoplasms	0.99
Major cardiovascular-renal diseases	1.01
Diseases of cardiovascular system	1.01
Vascular lesions affecting central nervous system	1.00
Rheumatic fever	0.92
Disease of heart	1.00
Chronic rheumatic heart disease	0.99
Arteriosclerotic heart disease, including coronary disease	0.98
Nonrheumatic chronic endocarditis and other myocardial degeneration	0.99
Other diseases of heart	1.10
Hypertensive heart disease	1.11
General arteriosclerosis	1.02
Other diseases of circulatory system	1.04
Chronic and unspecified nephritis and other renal sclerosis	1.02
Influenza and pneumonia, except pneumonia of newborn	0.94
Influenza	1.04
Pneumonia, except pneumonia of newborn	0.93

*Ratio of deaths in the 10 per cent sample for 1958 classified by the Seventh Revision to deaths classified by the Sixth Revision.
Source: National Office of Vital Statistics, Annual Summary for 1958, Part 2, vol. 7, no. 13, July 22, 1959.

Data on recent trends in diabetes mortality in various countries are given in table 7. For most countries the data cover the years 1950 to 1957. The trend of the death rate in this country over this period has not been consistent, but the average for the second half has been slightly below that for the first half. In Canada no distinct trend is apparent. A great part of Western Europe has experienced an increase in diabetes mortality recently, for example, the German Federal Republic, Austria, France, Belgium, Denmark and Italy. In a few countries, such as Switzerland and Sweden, there has been no marked change in the rate, while in a few cases, notably England, the trend has been downward. In both Australia and New Zealand the general trend has been downward also.

Two of the three countries in Asia for which data are shown show a generally rising trend in diabetes mor-

TABLE 7

Death rates per 100,000 from diabetes mellitus in various countries, 1950-1957

Country	1957	1956	1955	1954	1953	1952	1951	1950
United States	16.0	15.7	15.5	15.6	16.3	16.4	16.3	16.2
Canada*	11.2	11.3	11.0	10.6	11.0	10.9	11.3	11.3
Germany								
Fed. Republic	11.8	11.6	10.5	10.0	10.7	11.1	§	§
Austria	9.4	9.3	8.0	7.2	6.9	§	§	§
Belgium	‖	24.5	23.9	24.0	22.6	14.6	§	§
Denmark	6.9	7.0	5.2	5.9	5.1	5.3	6.8	§
Finland	8.7	6.0	5.7	4.9	6.2	6.0	5.9	5.4
France	12.0	12.7	11.8	11.3	11.5	10.8	10.5	9.2
Ireland	7.4	7.1	6.9	6.8	7.2	6.5	8.4	7.4
Italy†	‖	11.8	11.1	12.3	10.0	9.7	8.1	§
Norway	‖	6.9	6.6	6.8	6.3	6.9	8.3	§
Netherlands	13.9	12.7	12.7	11.9	11.2	11.4	11.4	8.5
Portugal	6.0	6.7	6.7	5.8	5.0	5.4	§	§
United Kingdom								
England & Wales	7.0	7.3	7.4	6.8	7.2	7.6	8.5	8.4
Scotland	9.8	9.2	8.9	8.7	8.6	9.3	10.9	10.9
Northern Ireland	6.4	6.4	7.0	7.5	5.9	5.5	6.4	6.8
Sweden	‖	10.1	9.9	10.3	10.9	12.0	10.5	§
Switzerland	‖	13.9	13.9	13.6	14.8	14.0	14.0	§
Australia	11.9	12.9	12.3	12.2	12.5	12.6	12.6	13.3
New Zealand‡	‖	10.5	10.2	9.8	12.6	11.8	13.3	12.7
Ceylon	‖	6.7	7.0	6.9	6.7	6.8	6.9	6.6
Israel, Jewish pop.	4.3	3.7	3.3	3.3	3.1	3.6	3.9	6.9
Japan	3.0	2.8	2.5	2.3	2.4	2.3	2.4	2.4

*1950-1955: Excluding Yukon and Northwest Territories.
†Since 1954, including Trieste.
‡Excluding Maoris.
§Data not available.
‖Data not yet available.
Source: World Health Organization—Epidemiological and Vital Statistics Reports. 1955-57—Vol. 12, No. 1, 1959, p. 11. 1950-56—Vol. 11, No. 3, 1958, p. 107.

tality. In Israel this applies more particularly to the period since 1953. The very low level of the rates there is notable. The death rates for Ceylon during the 1950's have been remarkably stable. The accuracy of the rates for that country is open to question for the reasons carefully set forth in a recent critical paper on the vital statistics of that country (Padley, R.: Cause-of-death statements in Ceylon—a study in levels of diagnostic reporting. *Bulletin of the World Health Organization* 20:677-95, 1959).

The enzyme, glucose-6-phosphatase, has been found in high concentrations in the liver, while lower levels of activity are present in the kidney and traces are found in the intestine. This enzyme is responsible for removing the phosphate from the 6 carbon of glucose, and for the release of glucose from the liver into the peripheral and hepatic circulation. Its activity has been found to increase in the liver of alloxan-diabetic animals.

R. L. Burt (*Am. J. Obstet. Gynec.* 74:551, 1957) noted that pregnancy induced a diabetogenic effect on carbohydrate metabolism, which was characterized by impaired peripheral utilization of glucose and resistance to insulin. The question arose as to whether these changes might be caused by increased levels of glucocorticoids occurring during gestation. It has also been reported by R. G. Langdon and D. R. Weakley (*J. Biol. Chem.* 214:167, 1955) that the administration of cortisone or adrenal cortical extract to mice increased the level of liver glucose-6-phosphatase.

Recently, R. L. Burt and N. Julian (*Am. J. Obstet. Gynec.* 77:6, 1959) studied the glucose-6-phosphatase activity in the liver of albino rats who were sacrificed on the seventeenth day of gestation. . . . In studying the livers of twenty-three pregnant rats for glucose-6-phosphatase activity, they found that an average of 5.25 ± 1.23 (mean ± standard deviation) mg. of inorganic phosphorus was released per gm. of liver. In thirty-one control animals, 6.98 ± 1.10 mg. of inorganic phosphorus was released per gm. of liver.

From *Nutrition Reviews*, Vol. 17, No. 8, pp. 245, 246, August 1959.

EDITORIALS

DIABETES AND MUCORMYCOSIS

Persons with diabetes are prone to develop bacterial and fungus infections. Of the latter, candidiasis (moniliasis) is not uncommon. Though mucormycosis is a less well-known complicating fungus infection, physicians treating patients with diabetes must have a clear knowledge of this mycosis and of the circumstances under which it develops.

Diabetes and leukemia are the two major conditions which predispose to mucormycosis. Less frequent are debilitating diseases and therapeutic agents such as steroids, antileukemic agents and antibiotics.[1] Diabetes induced by steroids employed therapeutically may be significant in the increased susceptibility of leukemic patients to the fungus infection.

In a series of forty-five cases of mucormycosis tabulated by the writer in 1957, diabetes mellitus with acidosis was the predisposing factor in eighteen (40 per cent). In a recent comprehensive review of mucormycosis diabetes was known to exist in twenty-two of 114 cases (19 per cent).[2] Of the twenty-two cases of diabetes, the head and neck structures were affected in sixteen (73 per cent), the lung in eight (36 per cent), and the gastrointestinal tract in one (5 per cent).

Mucormycosis is a relatively new disease in the United States. There are cases in the literature prior to 1943, in this country and in Europe, but the reports are often incomplete. The disease is undoubtedly more prevalent today than the number of reported cases suggests. Mucormycosis is unique because of its rapid fatal course, the presence of vascular thrombosis and infarction and the absence of the chronic inflammation and fibrosis of other deep fungus infections. Many cases have been recognized first at autopsy.

Cerebral Mucormycosis. The classical report of three fatal cases of mucormycosis in diabetic patients in this country appeared in 1943.[3] These developed in patients in diabetic acidosis, and led to death rapidly, in two to five days. The clinical course was characterized by orbital swelling. At autopsy the vessels of the meninges were found to contain unusually broad fungus filaments. The fungus had entered by the nose, infected the antrum and orbit on one side and extended by blood vessels to the meninges and frontal lobes of the brain. The fungus penetrated arteries and produced thromboses. This led to infarction, and the swelling of the orbit and the softening of the frontal lobes of the brain were a combination of infection and infarction. The disease was called mucormycosis because the broad, branching, nonseptate (no cross-bars) hyphae resembled those of *Mucor.* However, the fungus was not grown in culture from any of these cases and the fungus was observed only in tissue sections. In 1955 the fungus *Rhizopus oryzae* was cultured from an air sinus of a similar fatal case of cerebral mucormycosis;[4] and probably the fungus in the 1943 case was *Rhizopus*, not *Mucor.* The literature contains numerous fatal cases of the cerebral form of mucormycosis, nearly all of which follow the pattern of the cases described in 1943. Thrombosis of an internal carotid artery as a result of extension of the fungi via the ophthalmic artery from the orbit has been present in many of the cases. Most of the truly cerebral cases have been fatal, but there is a recent report of the survival of a patient with central nervous system mucormycosis who exhibited aphasia and hemiparesis.[5]

The term rhinomucormycosis has recently been given to the infection of the nose and paranasal sinuses which usually, but not always, leads to cerebral involvement.[6] The presenting signs may be neurologic, with loss of function of the fifth and seventh cranial nerves and with unilateral blindness. Diabetes mellitus has been the most frequent underlying disease. An important physical sign is the gray-black appearance of the infarcted nasal mucosa which resembles dried clotted blood. The disease must be considered whenever in uncontrolled diabetes there is a bloody nasal discharge, facial or orbital pain, lid drop, localized anesthesia about the eye, proptosis of the eye with limitation of motion of the bulbus oculi, fixation of the pupil, and loss of vision. A cloudy sinus on X-ray study, without fluid level, and lethargy progressing to coma, make the clinical diagnosis of rhinomucormycosis possible. Biopsy and culture of the nasal mucous membrane confirm the diagnosis and permit treatment to be instituted before the onset of cerebral fungus disease. Two patients with rhinomucormycosis have survived the disease and are still living, and there are undoubtedly others not reported

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(figure 1).[3] *Rhizopus* has been the most frequent etiologic fungus agent.

FIG. 1. Mucormycosis: A, orbital swelling of left eye; B, unilateral sinusitis. Nonfatal case in diabetic patient. (Reproduced, by permission, from J.A.M.A. 163, 805, 1957.)

Pulmonary Mucormycosis. Diabetes was the predisposing factor in four of the ten autopsy cases of pulmonary mucormycosis which the writer reported.[7] Primary pulmonary mucormycosis develops from fungus growth in the bronchi. Organisms penetrate the walls of bronchi and infect the hilar tissues. The fungus then invades the pulmonary artery and vein and causes thrombosis which results in pulmonary infarction. To a less extent pulmonary mucormycosis is a lobular pneumonia representing inflammatory response to the presence of the fungus. As the infarct develops there is pain, pleural friction rub and bloody sputum. In some cases the consolidation may form insidiously. Fever and leukocytosis are present. Roentgenograms reveal pulmonary consolidation. The duration of the mycosis in the ten reported cases, all fatal, varied from three to thirty days.

Two cases of pulmonary mucormycosis have now been reported in which a pulmonary focus has been removed surgically, one from a diabetic patient, with eradication of the disease and survival of the patients.[8,9]

Other Forms of Mucormycosis. Intestinal mucormycosis presents as hemorrhagic, gangrenous segments in the ileum or large intestine.[3] A case of cutaneous mucormycosis in a twenty-six-year-old white man with moderately severe diabetes took the form of a large ulcer of the ankle.[10] The ulcer healed completely in four months with oral administration of potassium iodide. Combined cerebral and pulmonary, and also systemic cases, occur.

The Causative Fungi. Mucormycosis has been defined by the study of organisms in microscopic tissue sections. Cultures have now been obtained from several cases. The most frequent organism recovered from human cases is *Rhizopus,* a ubiquitous mold on bread and fruit not ordinarily pathogenic and usually considered a laboratory contaminant.[2] It grows rapidly as a cottony mycelium and is characterized by root-like structures which extend from the hyphae (filaments) at the points where sporangiophores arise to be capped by sporangia containing spores the size of red blood cells. Only the broad filaments are seen in lesions. *Mucor* and *Absidia* have been recovered from some of the human and animal cases of mucormycosis. Thus, human mucormycosis is usually caused by *Rhizopus* rather than *Mucor.* However, mucormycosis continues to be a satisfactory designation of the disease because the family *Mucoraceae* contains the three genera already mentioned. It has been suggested that the disease be called phycomycosis or phycomycetous infection, because the *Phycomycete* fungi are characterized by lack of septation, and *Rhizopus, Mucor* and *Absidia* belong in this group.

In most cases of mucormycosis the broad nonseptate hyphae alone are present. In others there are bacteria with the fungus. Mucormycosis may occur in one portion of the lungs and aspergillosis in another.

Why Does Diabetes Predispose to Mucormycosis? The mode of action of diabetes in predisposing to this fungus infection has been the basis of extensive experimental studies. It seems clear that hyperglycemia is of far less importance than uncontrolled and acidotic diabetes. Rabbits and mice with chronic alloxan diabetes are as resistant as normal control animals to experimental *Rhizopus* infection. However, in the acutely toxic state of alloxan diabetes fulminating mucormycosis can be produced.[11] It can not be stated at present why this is possible—the inflammatory cellular response appears to be adequate in combating the infection.[12] Moreover, it is premature to single out acidosis as the most important feature of the predisposition.

Diagnosis. Mucormycosis is recognized in cases of diabetes by the striking appearances in the nose and about the orbit. Diagnosis is confirmed by examination of tissue biopsy of palate, nasal mucous membrane and lung and by culturing of tissue from these sites. In most cerebral cases the fungus has not been demonstrated in spinal fluid. Since the causative organisms are laboratory contaminants it is desirable to demonstrate the organism in tissue sections. There is no satisfactory skin or serologic test.

Treatment. The most important step in the treatment of mucormycosis is regulation of the diabetes with correction of the acidosis. Surgical excision of localized pulmonary lesions may be considered as adjunctive treatment. Potassium iodide therapy may be of assistance. Mycostatin was considered beneficial in one case.[6] Amphotericin B prevents the development of

Rhizopus infection in experimental animals and may be of value in human cases.[13]

ACKNOWLEDGMENT

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FAT CONTENT OF THE DIABETIC DIET

What is the optimum fat content of the diet for the patient with diabetes mellitus?

In order to answer this question, it becomes important to review periodically the new information and to assess more fully the necessity for a change in opinion with the progress of time. Much of the discussion that one hears in this area is speculative. The hope for diminishing the area of speculation lies in further research to develop factual knowledge.

The basic component of any diet is its caloric content. An individual may consume optimum amounts of the micronutrients, the minerals and other ancillary food factors, but unless his caloric demands are satisfied, he will starve. To achieve adequate caloric intake for any individual, the diet prescription must contain sufficient amounts of carbohydrates, proteins and fats. In the case of the patient with diabetes the amount of carbohydrate prescribed has definite limitations. When the carbohydrate content of the diabetic diet exceeds approximately 250 gm. in a day, the control of the glycosuria and the glycemia is in most cases made more difficult with the insulins currently available. For those who are not concerned with the control of the glycosuria as part of their therapeutic regimens for the patient, the loss of glucose in the urine becomes an important factor. In an attempt to assess the total caloric metabolic mixture, it is not the amount of carbohydrate that is taken by mouth that is important, but the actual amount of carbohydrate which is metabolized in the body, i.e., the difference between the amount consumed and the amount excreted in the urine. If one assumes that approximately 250 gm. of carbohydrate are metabolized, this will account for 1,000 calories. The average consumption of protein in the current diet for the diabetic patient varies from 70 to 100 gm. each day. This will account for another 400 calories, a total of 1,400 calories. The difference between the total caloric requirements and the 1,400 calories supplied by the carbohydrates and protein must be derived from fat. Thus the total fat content of the diet will vary considerably with caloric requirements of different individuals and cannot be limited to any fixed percentage of the total calories supplied by any specific diet prescription. One hundred grams of protein, as consumed by the average American, carries with it an inherent 40 to 50 gm. of animal fat. These fats are usually the more saturated type and supply about 360 calories. The remainder of the needed calories must be supplied by the visible or table fats and

Members of the Committee on Food and Nutrition who reviewed this statment are: Charles S. Davidson, M.D.; Norman Jolliffe, M.D.; Laurance W. Kinsell, M.D.; Harvey C. Knowles, Jr., M.D.; Fredrick J. Stare, M.D.; Francis D. W. Lukens, M.D.; Garfield G. Duncan, M.D.; William H. Olmsted, M.D.; Dwight Wilbur, M.D.

oils. These, generally speaking, are employed as spread for bread, in cooking and other food preparation, in salad dressing, and the fat component of the dairy products which are consumed daily.

Increasing attention has been paid to the place of the polyunsaturated fatty acids in the diet by virtue of their ability to reduce the concentration of the circulating cholesterol, and possibly to affect the beta lipoprotein fractions in the blood. While the total cholesterol concentration of the serum is found frequently to be elevated in those patients suffering coronary occlusions, it must be re-emphasized that up to the present writing there is no conclusive evidence that lowering the concentration of cholesterol in the circulating blood influences the atherogenesis. No one can deny that the concentration of cholesterol in the circulating blood is a most important suspect as a cause for atherogenesis. Many physicians are concerned now with the importance or necessity of incorporating the vegetable oils, with their high linoleic acid content, into the daily dietary of their patients. This must be done by substitution for the other types of fats or oils, rather than as an additional source of calories.

There are numerous reports of ways of reducing blood cholesterol concentrations: the administration of glycine, of neomycin, nicotinic acid, thyroxin, low-fat diets, polyunsaturated fatty acids, sitosterol, and undoubtedly others. The mechanisms of their actions are not definitely known, and may vary considerably. The substitution by the polyunsaturated fatty acids in the diet for the more saturated fats and oils offers the possibility of controlling the levels of circulating blood cholesterol without having to resort to supplementary medication or unusual dietary practices. In greatly hypercholesterolemic patients, these latter measures may be of extreme importance. For the individual whose problem is mainly prophylactic, the dietary methods of control are important because of their basic simplicity.

There are many means of introducing the polyunsaturated fatty acids into the diet in addition to the use of the vegetable oils. These include the use of nuts, the preference for chicken and fish over some of the other protein sources.

Studies in weight reduction of obese, middle-aged persons have led to the conclusion that the reduction of the weight itself may not be of prime importance in lowering serum cholesterol. When the patient comes into caloric balance at a new and lower level, this effect may be lost.

The fact that one can obtain so much better control of the glycosuria and glycemia with diets relatively high in fat content than with diets whose carbohydrate content is high, leads one to consider the use of the comparatively fat-rich diet for the diabetic patient. This can be acceptable to many physicians if it includes adequate quantities of the vegetable oils, such as cottonseed or corn oils, which have a high content of polyunsaturated fatty acids.

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BOOK REVIEWS

THIRST. *By A. V. Wolf. $12.50, pp. 536, Charles C Thomas, Springfield, Illinois, 1958.*

This manuscript deals with all aspects of thirst. In the preface the author states that he is attempting to assemble current knowledge of thirst in one review, and the purpose is accomplished in admirable fashion. The book is divided into two parts; one dealing with physiology, and the other with actual accounts of persons suffering from thirst.

Chapter I concerns basic subjects, such as the water content of the body, and how much water different species imbibe daily. It is of some interest to know that the cow drinks forty-five liters daily, the elephant 149 liters daily, and the rat only 35 cc. per day. The maximum gulp of a man is 30 cc., while an elephant can quaff 6.6 L. at one swallow. However, man can make up for his deficiency by carrying out sixty gulps a minute, in contrast to only twelve for the elephant. The remainder of the chapter contains a discussion of osmotic pressure, as viewed by the biologist. This section is worth reading by anyone interested in theories of tonicity.

In chapter II are given and discussed the many stimuli and processes thought to initiate thirst. All possible causes of thirst are presented, even the pleasures of love. Several older case reports are given wherein the subjects were observed *never* to drink any water! Of course they drank wine and other similar beverages, but this was for effect only. These unusual subjects are called "oligopotes." There is an interesting case report of a woman who never drank anything at all and is called an "apote." Thence the author goes into a discussion of the physiology of thirst. The theories of the dry mouth, cellular dehydration, and central stimulus are discussed at length. There are descriptions of the thirst brought on by dipsogens such as alcohol, states of sodium and potassium deficiency, and trauma and battle stress. The reader can only conclude that the sensation of thirst may arise from a multitude of causes, with mechanisms anything but clear.

In chapter III there is an account of satiety. The author finds difficulty in defining satiety, and states that one could follow Darwin in his remarks on definition, when he said

"I will not attempt a definition . . . everyone knows what I mean. . . ." It appears that thirst and satiety are very different problems. For example, a dog with an esophageal external fistula will stop drinking when the stomach is inflated with a balloon. Fluid ingestion is determined by many factors other than simply that of establishing normal tonicity of body fluid.

Chapter IV concerns the regulation of fluid volume. The current concepts of volume receptors are well covered. However, the author is not certain that volume alterations per se can be incriminated as causative agents in thirst or satiety.

Chapter V is a fascinating account of problems of thirst. It is stated that the maximum tolerance of man for water deprivation is about 20 per cent of his weight, whereas the slug may endure water loss equal to 75 per cent of its weight. The chemical findings of water deprivation are discussed, along with descriptions of the classical experiments of McCance, Elkington, and others. The pros and cons of drinking sea water are weighed. Though no definite conclusion is reached, the majority of opinion quoted appears to condemn this practice. No conclusions are given either concerning the ingestion of fish, though tables of fish composition are available.

The book is recommended to all interested in physiology. The author succeeds in his efforts to accumulate and assemble information about thirst.

CHEMISTRY OF PANCREATIC DISEASES. *By Harris Busch, M.D., Ph.D. $5.25, pp. 160, Charles C Thomas, Springfield, Illinois, 1959.*

Although the practicing physician is naturally and most immediately concerned with procedures that aid him in the diagnosis and treatment of his patients, he cannot resist a curiosity about the basic mechanisms of disease. Moreover, he realizes that what may be an interesting but seemingly irrelevant consideration at the moment can become a cogent and practical matter in the near future.

To the growing number of general books that describe the biochemical bases of disease, the present short volume on the pancreas by Dr. Harris Busch is a most welcome addition. The discussion is divided into three main parts: I. Chemistry of the exocrine diseases of the pancreas with chapters on the metabolism and exocrine secretions of the pancreas and on the biochemical aspects of acute pancreatitis and pancreatic insufficiency; II. Chemistry of the endocrine diseases of the pancreas with two main chapters on hypoinsulinism and hyperinsulinism; III. Neoplasia in the pancreas.

The aspects of basic biochemical interest are judiciously combined with those of clinical applicability. For example, the metabolism of the pancreas on a cellular level is described in chapter I, and the biochemical effects of insulin are considered in terms of enzyme mechanisms in pages 91-98 of chapter VI. General consideration is given to the diagnostic use of serum enzyme levels in acute pancreatitis (pages 56-58) and of analyses of stools and of ingested labeled protein and fat in pancreatic insufficiency (pages 65-72). Principles for the treatment of pancreatic insufficiency (pages 74-78) and diabetes (pages 103; 110-18) are briefly outlined.

Dr. Busch's book is admittedly not a text, and the practicing physician will be acquainted with a number of the clinical and laboratory features that are presented. Nonetheless, it is warmly recommended to the internist and to all others who are concerned with diseases of the pancreas, for it surveys in lucid fashion the present biochemical borders that will be the core of future knowledge of the diseases of this organ.

THE TREATMENT OF DIABETES MELLITUS. *By Elliott P. Joslin, Howard F. Root, Priscilla White, and Alexander Marble. $16.50, pp. 798, tenth ed., Lea & Febiger, Philadelphia, 1959.*

This book is to diabetes mellitus what the Encyclopaedia Britannica is to knowledge in general and, as past reviewers have noted, the task of reviewing it is formidable. The format, number of pages, and, in general, the method of presentation and chapter headings are similar to the previous edition. The same wealth of exhaustive detail, carefully updated, is presented with authority.

Whether one agrees with the Joslin group's approach to the subject or not, one is not left in doubt regarding their basic philosophy. Their viewpoint at the outset is succinctly stated by Dr. Joslin himself, who concludes the introductory chapter dealing with present concepts of diabetes with: "We still believe the pancreas underlies all diabetes, either because of the disease in it or because of its involvement by influences in the pituitary, adrenals, thyroid or liver. Even the advent of oral treatment has not changed our conviction." Also the conviction that control and absence of vascular and neurologic complications have a cause and effect relationship is forcefully set forth in this edition's preface: "One still reads that retinitis, nephropathy and neuritis bear no relation to control, but our detailed investigation of diabetics who have come under our own supervision proves the contrary."

These statements representing the philosophy of the Joslin group are the unifying feature which ties the individual chapters into a whole. There is one exception to this in an excellent chapter on the physiology of diabetes mellitus written by Dr. Albert E. Renold. This chapter distinguishes between "the endocrine defect (one or several) . . . and the metabolic defect (one or several)." With reference to the endocrine defect, Dr. Renold concludes that "the diabetic syndrome is the result of either absolute or relative insulin deficiency. This in no way precludes, however, the presence of additional features or anomalies in all or some forms or cases of diabetes." This chapter is followed by Dr. Marble's presentation of applied physiology with reference to insulin and blood sugar.

A new and timely chapter dealing with the oral hypoglycemic agents is presented by Drs. Marble and Leo P. Krall. Following introductory and historical comment, the experience and results of the Joslin Clinic with various agents are discussed. The authors stress that any conclusions are tentative, and conclude that perhaps the greatest contribution of these agents has been the impetus to research in diabetes.

As in previous editions, much of this book teaches by an impressive collection of statistical data. One can only admire the studious care in the collection of so much data over so many years. However, this reviewer feels compelled to comment that the statistical method has many limitations, and out of statistics emerges a picture scarcely, if ever, encountered clinically when the physician is handling an individual human being with diabetes mellitus. This statistical approach sets the tone of the book, and perhaps accounts for the fact that the only mention of psychological problems occurs in Dr. White's chapter concerning diabetic children and their later lives. It seems to this reviewer that future editions would be enhanced by an expert discussion of the emotional aspects not only associated with diabetes mellitus itself, but also involving iatrogenic and parental (in the case of children) factors.

ABSTRACTS

Beaven, Donald W.; Nelson, Don H.; Renold, Albert E.; and Thorn, George W. (Depts. of Medicine, Harvard Medical School and Peter Bent Brigham Hosp., Boston, Mass.): DIABETES MELLITUS AND ADDISON'S DISEASE: A REPORT ON EIGHT PATIENTS AND A REVIEW OF 55 CASES IN THE LITERATURE. New England J. Med. *261*:443-54, Aug. 27, 1959.

Six as yet unreported cases with established diagnoses of Addison's disease and diabetes mellitus are described, and follow-up observations on two previously reported cases are presented.

The literature is surveyed, and fifty-five cases previously reported are reviewed together with the above-mentioned eight cases. The cases are divided into three groups for the purpose of this review: Addison's disease preceding diabetes mellitus; diabetes mellitus preceding Addison's disease; and simultaneous onset of both conditions.

The possibly increasing incidence of diabetes in patients with Addison's disease is discussed. W.R.K.

Buckman, Lewis T. (Editorial): IDENTIFICATION OF THE DIABETIC. Pennsylvania M. J. *62*:1551-52, October 1959.

The need to identify the diabetic has long been recognized; also that cards have a limited value—they wear out, are lost or forgotten. They are not practical for the diabetic child who does not carry a wallet or handbag.

Even the composed, level-headed layman may hesitate to go through the pockets of a comatose man or the handbag of a comatose woman in the street, in the theater, in the store, or in church. Such search is usually delegated to the policeman, the fireman, or the physician who may happen by. And the card may be missed in the welter of licenses, credit cards, insurance identification, and certificates of membership in all sorts of organizations.

An identification disk, to be worn as a locket, as a bangle on a bracelet, or a wrist band, as a watch face—such a thing as can readily be attached to a child's wrist for safe and sure identification—is to be preferred. W.R.K.

Burt, Richard L.; and Pulliam, Robert P. (Dept. of Obstetrics and Gynecology, Bowman Gray Sch. of Medicine, Wake Forest Coll., and North Carolina Baptist Hosp., Winston-Salem, N.C.): CARBOHYDRATE METABOLISM IN PREGNANCY: LACTIC ACID PRODUCTION FOLLOWING INSULIN ADMINISTRATION. Obst. & Gynec. *14*:518-22, October 1959.

Peripheral blood lactate levels after a standard dose of insulin are significantly decreased in pregnancy in association with lessened hypoglycemia and hypophosphatemia. This diabetogenic effect of gestation is interpreted as due to a metabolic block, possibly at the hexokinase level. W.R.K.

Butterfield, W. J. H.; and Holling, H. E. (Med. Res. Council's Clin. Res. Unit, Guy's Hosp., London, England): PERIPHERAL GLUCOSE METABOLISM IN FASTING CONTROL SUBJECTS AND DIABETIC PATIENTS. Clin. Sc. *18*:147-74, 1959.

The methods used to estimate the uptake of glucose by the forearm tissues, predominantly muscle, are described in detail and the errors involved defined. The uptake was deduced from arterial and venous blood sugar levels and simultaneous blood flow measurements. Studies were carried out in hospital in six nondiabetic subjects and twelve patients comprising four stable diabetics, five patients with severe diabetes and three brittle diabetics, all fasting and in bed. It was found that:

The arterial blood sugar level was relatively stable except in patients with "brittle" diabetes.

The forearm blood flow was so variable that its simultaneous measurement was necessary to deduce tissue uptake accurately.

The arteriovenous blood sugar difference was usually positive in nondiabetic subjects and stable diabetics. It was sometimes negative in brittle diabetics and frequently so in severe diabetics. The incidence and magnitude of such negative arteriovenous differences in severe diabetics were significantly different from the results in controls and blood duplicates.

There was a positive correlation between arterial blood sugar and tissue uptake, which was statistically significant in cases where the variations of arterial blood sugar were large.

There appeared to be a "threshold" level of blood sugar above which glucose entered the forearm tissues from the blood and below which glucose passed in the reverse direction. The latter circumstances were generally obtained in fasting severe diabetics with glycosuria.

The rate of transport of glucose into and out of the forearm tissues was proportional to the differences between the arterial blood sugar and this "threshold." Insulin lowered this threshold.

The factors regulating the fasting blood sugar and the arteriovenous sugar differences of diabetic patients are considered in the light of these findings. W.R.K.

Colwell, Arthur R., Jr.; and Levine, Rachmiel (Northwestern Univ. Med. Sch., Chicago, Ill.; Michael Reese Hosp., Chicago, Ill.): TREATMENT OF DIABETES: INSULIN THERAPY: ORAL THERAPY. Postgrad. Med. *24*:564-67, November 1958.

An exposition of personal viewpoints of the authors on the clinical use of sulfonylureas in practice. Some controversial questions regarding the scope of their application were discussed. W.R.K.

Daniels, Robert S. (Dept. of Psychiatry, Univ. of Chicago Coll. of Med., Chicago, Ill.): LATE ADOLESCENCE IN A JUVENILE DIABETIC: A CASE REPORT. J. Clin. & Exper. Psychopath. *20*:231-34, September 1959.

A case of juvenile diabetes mellitus is presented to demonstrate the characteristic emotional and diabetic instability often seen in late adolescence. The similarity of the conflicts at the onset of the diabetes and its exacerbation in adolescence is noted. The therapeutic process is described with evidence that diabetic control may once again be instituted if the conflicts are partially resolved. W.R.K.

DeLawter, DeWitt E.; Moss, James M.; Tyroler, Sidney; and Canary, John J. (Dept. of Medicine, Georgetown Univ. Med. Sch. and the Diabetic Clin., Georgetown University Hosp., Washington, D.C.): SECONDARY FAILURE OF RESPONSE TO TOLBUTAMIDE TREATMENT. J.A.M.A. *171*:1786-92, Nov. 28, 1959.

The significant findings of a follow-up study of nonketotic diabetic patients treated with tolbutamide (Orinase) are as follows:

In a group of 200 patients who received tolbutamide and were followed for up to three years the rate of secondary failure of response to the drug was 29.5 per cent. In the first year the rate of failure in the same group of patients had been 16 per cent.

Patients with poor and fair initial diabetes control develop secondary failure sooner than those with good and excellent control.

There was no significant change in the insulin requirements of patients before treatment with tolbutamide and after their secondary failure of response to the drug.

Only two of the twenty-five who were given a retrial on tolbutamide therapy obtained a good response. Therefore, it can be anticipated that once a patient fails to respond to the drug the failure will be permanent.

A satisfactory response to treatment with chlorpropamide (Diabinese) or metahexamide (Euglycin) was obtained in 20 per cent of the patients in whom secondary failure of response to tolbutamide had occurred. Phenethylbiguanide (DBI) gave a satisfactory response in 55 per cent of these.

All mature, nonketotic diabetics whose condition cannot be controlled by diet alone deserve a trial on tolbutamide therapy. These patients must be followed up at least every two months, because they may develop secondary failure with little warning and no apparent cause. W.R.K.

Ditzel, Jørn; and Moinat, Pierre (Baker Clin. Res. Lab., Harvard Med. Sch., Joslin Clin., and Dept. of Biology, Boston University Graduate Sch., Boston, Mass.): CHANGES IN SERUM PROTEINS, LIPOPROTEINS, AND PROTEIN-BOUND CARBOHYDRATES IN RELATION TO PATHOLOGIC ALTERATIONS IN THE MICROCIRCULATION OF DIABETIC SUBJECTS. J. Lab. & Clin. Med. *54*:843, December 1959.

In order to evaluate the relationship between the incidence of intravascular erythrocyte aggregation ("sludged blood") and the presence and severity of retinopathy and nephropathy, direct biomicroscopic observations of the microcirculation in the conjunctival vascular bed were made in seventy asymptomatic, supposedly healthy children and 145 young diabetics, with and without retinal and renal complications. It is found that intravascular erythrocyte aggregation occurs far more frequently and more extensively in the diabetics than in the nondiabetic controls. With increasing degrees of diabetic vascular complications there is an increasing tendency for the occurrence of generalized erythrocyte aggregation in vivo with slowing of blood flow in the small blood vessels.

Comparative studies were made relating the degree of intravascular erythrocyte aggregation to the composition of the serum proteins, lipoproteins, and protein-bound carbohydrates as determined by paper electrophoresis. In 157 determinations, a significant relationship was shown between intravascular erythrocyte aggregation (I.E.A.) and an increase in α_1, α_2, and β globulins and a simultaneous decrease in the albumin fraction of serum. One hundred and twenty-eight serum lipoprotein determinations show a correlation between the degree of aggregation and the amount of total lipoprotein and its two component fractions, α and β lipoproteins. One hundred and eighteen serum protein-bound carbohydrate determinations show no direct relationship between their component fractions and the degree of aggregation.

A correlation is present between the incidence of intravascular erythrocyte aggregation and the presence of vascular pattern changes I and II in the conjunctival vascular bed. This correlation suggests that both the aggregation phenomenon, i.e., the protein changes, as well as the vascular pattern changes, are independent manifestations of tissue responses to acute alterations in the metabolism of the diabetic subjects. W.R.K.

Editorial. GLYCOGEN METABOLISM. J.A.M.A. *171*:1966, Dec. 5, 1959.

Concepts of the enzymatic reactions responsible for the biosynthesis of polysaccharides have been completely changed in the past ten years as a result of the discovery of uridine nucleotides. According to recent reports, uridine diphosphate glucose is the key intermediate in the synthesis of glycogen.

The discovery that uridine diphosphate glucose participates in the synthesis of glycogen indicates a hitherto unsuspected pathway for the formation of glycogen from glucose-1-phosphate. Earlier investigations indicated that glycogen is formed by the following reaction:

1. Glucose-1-PO_4 + $\rightleftarrows$ glycogen + PO_4 phosphorylase

The more recent publications suggest that glycogen is formed as follows:

2. Uridine-diphosphate glucose $\rightleftarrows$ glycogen + uridine diphosphate.

It thus appears that both reactions 1 and 2 represent pathways for the formation of glycogen from glucose-1-phosphate. However, the difference between the equilibriums of the two reactions suggests that reaction 1 may be a more suitable pathway for the breakdown of glycogen whereas reaction 2 may be more suitable for glycogen synthesis. Since both epinephrine and glucagon have been shown to be involved in the activation of phosphorylase, the enzyme catalyzing reaction 1, the ability of these two hormones to make glucose available may be explained by this reaction.

The discovery of the role of uridine diphosphate glucose in glycogen synthesis opens new avenues for the study of carbohydrate metabolism. It seems likely that unexplained phenomena related to disturbances in human carbohydrate metabolism may find explanation as disturbances of this new pathway. The possible role of hormones in regulating the rate of these enzymatic reactions needs elucidation. W.R.K.

Editorial. THE PRESENT SITUATION IN THE TREATMENT OF DIABETES. J. Louisiana M. Soc. *111*:404-05, October 1959.

The oral hypoglycemic preparations, in general, are to be avoided in juvenile diabetics. They are not to be depended upon exclusively in the treatment of very unstable diabetics or during complications. They are not to replace careful adherence to diet. It is apparent, at this time, that diet and systematic management are still the fundamentals of the treatment of diabetes. To these should be added, when indicated, insulin or the oral hypoglycemic drugs, or both. W.R.K.

Elrick, Harold; Whipple, N.; Arai, Y.; and Hlad, C. J., Jr. (Research Labs. and Radioisotope Service of Veterans Administration Hosp. and Dept. of Med., Univ. of Colorado Sch. of Medicine, Denver, Colo.): FURTHER STUDIES ON THE RENAL ACTION OF GLUCAGON. J. Clin. Endocrinol. *19*:1274-81, October 1959.

Studies of the action of glucagon on the renal excretion of uric acid, total nitrogen and urea nitrogen are reported. A single dose of glucagon was administered to each of fourteen

normal subjects and four patients with gout. Seven normal subjects who received glucose infusions served as controls. In addition, two of the patients with gout were given glucagon three times daily for several days while they were receiving a constant diet. Glucagon caused an immediate increase in uric acid excretion which persisted at least one hour. However, this increase in uric acid was not detected in twelve-hour urine collections from two patients receiving three daily injections of glucagon. Evidence is presented that the immediate uricosuric effect is not secondary to the hyperglycemic action of glucagon and that it may be due to an action on the renal tubule. Administration of glucagon resulted in a significant but small increase in total nitrogen and urea nitrogen excretions. Because these changes closely paralleled changes in endogenous creatinine clearance they are considered secondary to variations in glomerular filtration rate. W.R.K.

Fair, John R. (Div. of Ophthalmology, Dept. of Surgery, Med. College of Georgia, Augusta, Ga.): OCULAR SIGNS OF DIABETES. J.M.A. Georgia *48*:410-13, August 1959.

The ocular complications of diabetes are a tribute to the success of modern treatment methods, since many years of life are required before they develop. Prior to the introduction of insulin, diabetics simply did not live long enough to experience the vascular degeneration that accounts for the well-known retinopathy, the cataracts, and the neuropathy that characterize the late stages of the disease.

The basic pathologic process responsible for diabetic retinopathy manifests itself in a tendency toward new blood vessel formation and hemorrhage. Retinopathy is not seen except in cases of diabetes of long standing. At least ten years of the disease are required to produce the vascular phenomena. Diabetics who acquire their disorder in childhood are especially likely to experience visual difficulty. The various stages of diabetic retinopathy require years to develop. There is some evidence indicating that the more rigid the control of the diabetes, the slower the appearance and progression of the retinal disease.

Certain other eye ailments are prone to occur in diabetes. Cataract is the most frequent and best known of these. New blood vessels may form on the surface of the iris in cases of severe diabetes of long standing (rubeosis iridis). Spontaneous rupture of these vessels is seen occasionally, the anterior chamber filling partially or completely with blood. Secondary glaucoma may follow with loss of any sight that remains or even loss of the eyeball. Diabetic neuropathy of the nerves to the ocular muscles is a well-known entity. Usually the third or the sixth nerve is involved. Pain may be considerable, simulating ruptured aneurysm of the circle of Willis.

Diabetes is only one of the many systemic diseases in which ocular changes feature prominently. Familiarity with the use of the ophthalmoscope and time taken to examine the outer eye carefully will often clarify diagnostic problems for the general practitioner and specialist alike. W.R.K.

Farquhar, Marilyn G.; Hopper, James, Jr.; and Moon, Henry D. (Depts. of Pathology and Med., Univ. of California Sch. of Med., San Francisco, Calif.): DIABETIC GLOMERULOSCLEROSIS: ELECTRON AND LIGHT MICROSCOPIC STUDIES. Am. J. Path. 35:721-53, July-August 1959.

Renal biopsy specimens from seven patients with diabetes mellitus were examined by light and electron microscopy. Clinically, the patients presented great variation in severity of renal impairment, ranging from three patients with normal renal function and blood pressure to two patients with the classical features of the Kimmelstiel-Wilson syndrome. By light microscopy diabetic glomerulosclerosis was characterized by gradual obliteration of glomeruli by the deposition of hyalin. Hyaline deposit was evident initially near the afferent arteriole and subsequently extended radially to involve more peripheral loops. By electron microscopy, thickening of the basement membrane proper was one of the earliest manifestations of the disorder. Finally, with further progression, the capillary lumen was obliterated. In the later stages, hyalin showed altered staining characteristics and was more heterogeneous in texture by electron microscopy. The nodular lesions developed from the diffuse lesions by enlargement of the hyaline deposits, as originally suggested by Bell. Fibrinoid deposits or "exudative lesions" of glomeruli were present in two patients with the most advanced glomerular alterations. This substance could be distinguished in electron micrographs by its great density. It was subendothelial in position, lying between the endothelial cell membrane and the basement membrane. The epithelium was not altered early in the course of hyaline deposition. Later, however, some loss of the epithelial foot processes was seen in severely damaged glomeruli. The fine structural alterations of glomeruli in diabetes mellitus could be differentiated from those occurring in disseminated lupus erythematosus, nephrosis, amyloidosis, and preeclampsia and eclampsia. W.R.K.

Fønss-Bech, P.; and Nielsen, Meta Damkjaer (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): THE SEPARATION OF THE A AND B CHAINS FROM OXIDIZED INSULIN: II. ZONE ELECTROPHORESIS IN A DENSITY GRADIENT. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:90-98, 1958.

The column electrophoresis apparatus combined with the TRIS-buffer and a sucrose density gradient gives under the described conditions, compared with zone electrophoresis on starch (Fønss-Bech and Skovsted 1958), a better separation of the two peptide chains from oxidized insulin and it is stated that the B peak is not a homogeneous peak, as confirmed by earlier tests for homogeneity. A great advance is that the zone electrophoresis in a density gradient is easy to carry out and that the concentrations of the peptide in the fractions can be determined direct by UV instead of using the Lowry reaction. W.R.K.

Fønss-Bech, P.; and Skovsted, Lis (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): THE SEPARATION OF THE A AND B CHAINS FROM OXIDIZED INSULIN: I. ZONE ELECTROPHORESIS ON STARCH. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:82-89, 1958.

The oxidized A and B chains of insulin were separated by zone electrophoresis on starch. The carbonate-bicarbonate buffer of *p*H 9.1 has proved useful for this purpose and evidence has been given for the purity of the two components. W.R.K.

Green, Robert C., Jr. (Dept. of Medicine, Community Memorial Hosp., South Hill, Va.): DIABETES MELLITUS SECONDARY TO PRIMARY CARCINOMA OF THE HEAD OF THE PANCREAS. South. M. J. 52:1211-13, October 1959.

From a review of the literature, nine authors, reporting on 762 patients with primary carcinoma of the pancreas, found 12 per cent of the total had diabetes discovered after the

onset of symptoms referable to pancreatic neoplasm. It is apparent that diabetes mellitus occurring secondary to primary carcinoma of the pancreas is more common than generally appreciated. An example of such an occurrence is reported. W.R.K.

Haabti, E. (Letter to the Editor) (Dept. of Clin. Chemistry, University Hosp., Turku, Finland): EFFECT OF INSULIN IN A CASE OF ESSENTIAL HYPERLIPEMIA. Scandinav. J. Clin. & Lab. Invest. *11*:305-06, 1959.

The patient was a thirty-three-year-old male with creamy lipemic serum. Diabetes, thyroid dysfunction and renal diseases were definitely excluded by normal laboratory tests. Forty units of Insulin Lente were given to the patient subcutaneously every morning at eight o'clock. The total lipids of the serum were determined every morning or every other morning. Forty units of Insulin Lente daily resulted in a sharp fall in the blood lipids. However, perhaps owing to improper dosage, hypoglycemia with a consequent increase in appetite and fat resorption caused a secondary rise in the lipemia after three days' treatment. A further increase in insulin dosage again caused a drop in the lipid values, but the hypoglycemic symptoms also became stronger, so that no prolonged treatment with insulin could be undertaken. However, in a later experiment with a smaller dose, 20 units of Regular Insulin every other day, a stable clearing was obtained for several weeks. W.R.K.

Hlad, Charles J., Jr.; and Elrick, Harold (Research Labs. and Radioisotope Service of Veterans Administration Hosp. and Dept. of Med., University of Colorado Sch. of Medicine, Denver, Colo.): FURTHER STUDIES OF THE KINETICS OF GLUCOSE UTILIZATION. I. A NEW METHOD OF DATA ANALYSIS. J. Clin. Endocrinol. *19*:1258-73, October 1959.

Evidence is presented to show that the extreme variation in rate constants for blood glucose disappearance reported by different laboratories is due to the use of an incorrect equation and/or an incorrect method of data analysis. It is demonstrated that graphic (semilog) methods are too insensitive to be used to justify equations describing blood glucose disappearance. The correct equation is shown to be one of exponential form containing an added constant term which in the normal subject is significantly less than the fasting level of blood glucose. A new method of data analysis (slope analysis) is described which results in the same specific rate constant, K, regardless of the equation employed. This method is made practical by the introduction of a mechanical slope reader which eliminates excessive calculations. W.R.K.

Hofstetter, J. R.; and Jaccottet, H. (Medical Policlinic, Univ. of Lausanne, Switzerland): ORAL TREATMENT OF DIABETES WITH A NEW HYPOGLYCEMIC AGENT, P-607: PRELIMINARY REPORT. Schweiz. med. Wchnschr. *89*:134-35, Jan. 31, 1959.

P-607 (chlorpropamide) is more effective than D-860 or BZ-55, but it is often not so well tolerated. In certain cases, the general condition of the patient improves considerably, which justifies the use of this new hypoglycemic drug. P-607 also produces increased sensitivity to alcoholic beverages. (French) G.R.C.

Huvos, Andrew; and Rocha, Heonir (Dept. Cardio-Respiratory Res., Walter Reed Army Inst. of Res., Washington, D.C.; Hosp. das Clinicas, Salvador, Bahia, Brazil): FREQUENCY OF BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS: A CONTROLLED STUDY. New England J. Med. *261*:1213-16, Dec. 10, 1959.

On the basis of clinical and autopsy studies showing a high incidence of urinary infections among diabetic patients many have long considered diabetes a predisposing factor to urinary infections. Most of these studies, however, lack direct controls, and fail to correlate the findings with the age and sex of the patients.

Twenty-four of the 100 patients had positive urine cultures; the difference between diabetic and control patients was not statistically significant. The incidence of positive cultures was significantly greater in elderly patients (30 per cent) than in the young (4 per cent). No significant difference between men and women in the incidence of bacteriuria could be demonstrated. *Escherichia coli*, alone or in combination with another gram-negative organism, was the pathogen most frequently encountered. No significant correlations between the presence of bacteriuria and certain clinical aspects of diabetes were observed. For the most part, the clinical and laboratory findings traditionally thought of as indicative of urinary infections were absent in patients with bacteriuria.

The data suggest that the patient's age is of much greater significance in the "epidemiology" of bacteriuria than the presence or absence of diabetes, in accordance with earlier findings.

A similarly decisive role of sex could not be conclusively demonstrated. Others found bacteriuria to be more frequent in females than in males. The present data show a similar difference, which, however, is not significant. A possible explanation for this may lie in the small number of male patients in this series.

A final epidemiologic consideration of great importance is that the entire group in this study consisted of hospitalized patients. Many of them had various chronic or acute illnesses.

In view of the growing evidence implicating the role of the catheter in the pathogenesis of urinary infections, it is interesting to note the large proportion of patients with bacteriuria in whom a past history of manipulations on the urinary tract could be obtained. The study also demonstrates the lack of associated clinical and laboratory findings in bacteriuria. Few laboratory tests of similar simplicity and low cost yield significantly positive results in such a high number of cases in a selected group of patients. W.R.K.

Keiding, Nils Rud. (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): PROTEIN-BOUND CARBOHYDRATES AND PROTEINS OF SERUM FROM DIABETIC PATIENTS AND THE RELATION TO THE LATE DIABETIC MANIFESTATIONS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:11-81, 1958.

In the light of our present knowledge it has to be recognized that no safe conclusions can be drawn concerning the correlation between the presence of late complications of diabetes and changes in serum protein and protein-bound carbohydrate.

The pattern of changes in serum protein and protein-bound carbohydrate presented in this investigation, in connection with the analysis given on the present state of knowledge of the protein-bound carbohydrate of serum, to a higher degree support the assumption that the changes seen in late diabetes are a manifestation of nonspecific reactions of the organism. A further evaluation of such changes primarily necessitates more basic and refined biochemical investigations, investigations

which should not necessarily be focused especially on the diabetic condition. W.R.K.

Kempner, Walter; Peschel, Ruth Lohmann; and Schlayer, Clotilde (Dept. of Med., Duke Univ. School of Med., Durham, N.C.): EFFECT OF RICE DIET ON DIABETES MELLITUS ASSOCIATED WITH VASCULAR DISEASE. Postgrad. Med. *24*:359-71, October 1958.

One hundred consecutive diabetic patients with hypertension were followed on a rice diet for an average of twenty-two months (three months to eleven years). This consisted of 565-570 gm. of carbohydrate, 20-25 gm. of protein, less than 5 gm. of fat and 120 mg. sodium. These were mainly maturity onset type of diabetics, ages nineteen to seventy-one (average age fifty-one) and using an average insulin dose of 25 units per day.

The specific diabetic retinopathy, even retinitis proliferans, was found to be improved in 25 per cent of cases. The insulin requirement did not increase with this high carbohydrate regimen and it actually decreased in forty-two out of the seventy-two insulin treated patients. W.R.K.

Kravitz, Charles H.; and Menin, William (Philadelphia, Pa.): CARCINOMA OF THE PANCREAS ASSOCIATED WITH DIABETES MELLITUS. Pennsylvania M. J. *62*:1332-34, September 1959.

From a study of the literature and a review of the cases admitted to the Albert Einstein Medical Center, Northern Division, over a ten-year period, it has become obvious that there is a greater incidence of carcinoma of the pancreas in individuals having diabetes mellitus. The carcinoma may appear months or years after the onset of diabetes mellitus; hyperglycemia may be a simultaneous accompaniment of the carcinoma or it may come late in the course of the disease. In any eventuality, it is the responsibility of the physician to rule out this entity in patients presenting a picture which at first glance seems to be diabetes mellitus. It is also essential that every known diabetic be viewed with suspicion when a status quo suddenly or gradually changes and cannot be explained by other factors. Every diagnostic aid should be employed, and since at best any or all of them may be inconclusive repetition of the tests is often necessary. W.R.K.

Lerman, Sidney (Div. of Ophthalmology, Univ. of Rochester, Sch. of Med. & Dentistry, Rochester, N.Y.): ENZYMATIC FACTORS IN EXPERIMENTAL GALACTOSE CATARACT. Science *130*:1473-74, Nov. 27, 1959.

The author reports in vivo and in vitro experimental work in rats indicating that inhibition by galactose-1-phosphate (gal-1-P) of the hexose monophosphate shunt pathway of essential glucose metabolism in the lens may be implicated in the pathogenesis of experimental cataracts.

The author's studies are based upon the finding by Schwarz and Goldberg that gal-1-P accumulated in the lens capsule and epithelium of rats fed a 30 per cent galactose diet. The concentration of this ester in such lens was observed to be ten times the amount present in normal lens and to approximate the order present in the red blood cells of humans suffering from congenital galactosemia. Kalckar has shown such individuals lack the enzyme galactose-1-phosphate uridyl transferase, necessary for the conversion of galactose to glucose in the step galactose-1-PO_4 $\rightleftarrows$ glucose-1-PO_4, whereby galactose enters the metabolic cycle.

The hypothesis that the presumptive accumulation of gal-1-P in galactose-fed rats might inhibit the hexose monophosphate shunt pathway of glucose metabolism in the lens was founded on Kinoshita's demonstration of the significance of this pathway in lens metabolism. Following the entry of glucose into this pathway by hexokinase-stimulated phosphorylation to glucose-6-phosphate, the latter first undergoes oxidation to 6-phosphogluconate in a reaction catalyzed by glucose-6-phosphate (G-6-P) dehydrogenase (involving triphosphopyridine nucleotide (TPN) as H receptor) and then the 6-phosphogluconate is oxidized to the 5-carbon keto-sugar, ribulose 5-phosphate, in a reaction catalyzed by 6-phosphogluconate (6-PG) dehydrogenase and again involving TPN as a co-factor and H receptor.

The author determined the relative activities of G-6-P and of 6-PG dehydrogenase in rats on the cataractogenic galactose diet at the time the first ophthalmoscopic evidence of cataract formation was noted and found a marked inhibition of G-6-P dehydrogenase activity. The activity of G-6-P dehydrogenase showed a significant decline on the fourth day of galactose feeding and continued to fall till the fourteenth day when it leveled off at 60 per cent of normal. This inhibition preceded by four days the inhibition of soluble protein synthesis in such lens, which is reported not to occur until the eighth day of galactose feeding: In vitro experiments upon the soluble protein fraction of homogenized lens also revealed a reduction of G-6-P activity with an average inhibition of 20 per cent.

It is thus concluded that inhibition of the hexose monophosphate shunt at the glucose-6-phosphate $\leftrightarrows$ 6 phosphogluconate step may be concerned in the pathogenesis of galactose cataracts. L.S.S.

McGavack, Thomas Hodge (Veterans Administration Center, Martinsburg, W. Va.): A CRITICAL APPRAISAL OF ORAL HYPOGLYCEMIC AGENTS. J. Am. Geriatrics Soc. 7:681-97, September 1959.

None of these oral hypoglycemic agents is a substitute for insulin. All of them act upon both the pancreas and the liver, but the nature of the activity is still obscure. They are useful in a small percentage of diabetics of the so-called "stable" type, who require both insulin and a well controlled diet to maintain optimal health. The long-term effects on the capacity of the pancreas to produce insulin and on the enzyme systems of the liver concerned with carbohydrate metabolism are not yet known. W.R.K.

Nakamura, K.; Shigeta, Y.; Wada, M.; and Yoshida, T. (First Dept. of Internal Medicine, Osaka Univ. Med. Sch., Osaka, Japan): SERUM INSULIN ACTIVITY AND METABOLIC ABNORMALITIES IN DIABETICS. M. J. Osaka Univ. *10*:151-58, August 1959.

Serum insulin activity of normal adults was found to be 101±46 mU./ml., while great variation existed in the serum insulin activity in diabetics. The serum insulin activity was much depressed in juvenile diabetics as compared to normal adults or maturity-onset diabetics. Diabetics having any complications showed generally diminished serum insulin activity. Close negative correlation was found between serum insulin activity and the rise of blood sugar following glucose loading, although no significant correlation was found between serum insulin activity and fasting blood sugar or serum total cholesterol. Negative correlation was noted between serum insulin activity and urinary excretion level of ketone bodies, and

positive correlation was found between serum insulin activity and acetylation of *p*-aminobenzoic acid. Oral hypoglycemic compounds such as mesoxalate and sulfonylureas were not very effective in diabetics with low serum insulin activity, but phenethyldiguanide combined with insulin was effective in some of these cases, reducing markedly the dose of insulin injection. W.R.K.

Nesbitt, Tom E. (Vanderbilt Univ., Nashville, Tenn.): GENITO-URINARY ASPECTS OF DIABETES. Am. Pract. & Digest Treat. 10:1158-63, July 1959.

A consideration of the relationship between urology and diabetes encompasses three fields: (1) infection, (2) neuropathic changes, and (3) a surgical phase. Various aspects of each are discussed. W.R.K.

Olloqui, F. Flores (Monterrey, Mexico): ORAL TREATMENT OF DIABETES MELLITUS. Rev. españ. enferm. ap. digest. *18*: 1093-1106, August-September 1959.

The writer amplifies the therapeutic trials carried out since 1956 with the use of the drugs BZ-55 (carbutamide) and D-860 (tolbutamide) in the treatment of diabetes mellitus. He comments on the percentage of satisfactory results and describes the toxi-allergic reactions exhibited by some patients. Some case histories of special interest are given in detail. W.R.K.

Pennock, L. Lewis (Pittsburgh, Pa.): CLINICAL EXPERIENCE WITH CHLORPROPAMIDE IN DIABETES. Pennsylvania M. J. 62:1537-39, October 1959.

Chlorpropamide, a new hypoglycemic sulfonylurea compound, has been successfully used in the treatment of 118 diabetics over a period of two to fourteen months. In this group of adult diabetics, 79 per cent were successfully controlled. Dietary control is essential for the treatment of all diabetics and chlorpropamide need not be used when diet alone is adequate. W.R.K.

Pomeranze, Julius; Mouratoff, George T.; Gadek, Raymond J.; and King, Edward J. (New York Med. College and Bird S. Coler Memorial Home and Hosp., New York, N.Y.): PHENETHYLBIGUANIDE, A NEW ORALLY GIVEN HYPOGLYCEMIC AGENT: REPORT AFTER TWO YEARS OF CLINICAL EXPERIENCE. J.A.M.A. 171:252-58, Sept. 19, 1959.

Phenethylbiguanide (DBI), a new synthetic, nonsulfonylurea compound, has proved to be an effective hypoglycemic and hypoglycosuric medicament for oral use in the management of diabetes mellitus.

In the study it was found that DBI could be used alone or with a reduced amount of insulin to manage 62 per cent of an unselected group of diabetic patients without regard for the class of diabetes. In 26 per cent of all the patients treated, although good hypoglycemic response was evident, gastrointestinal side effects necessitated the withdrawal of DBI. However, the incidence of side effects has been reduced in more recent experience by newer dosing technics. DBI therapy was discontinued in the remaining 12 per cent of patients in these studies for reasons not related to the effectiveness or side reactions of the drug.

The sole limitation on the already broad clinical applications of DBI appeared to be its gastrointestinal side effects. No organ toxicity has been observed in any patient, including those who have been maintained on this therapy for periods ranging through two years. W.R.K.

Ranke, Eugene J. (Dept. of Medicine, Univ. of Illinois College of Med., Chicago, Ill.): DIABETIC RETINOPATHY AND THE PITUITARY. A.M.A. Arch. Ophth. 62:859-63, November 1959.

The incidence of diabetic retinopathy in pituitary tumor patients is 3.0 per cent in this series. The incidence of diabetic retinopathy in diabetic patients with pituitary tumor is 6.7 per cent and in a similar group of diabetic patients without pituitary tumor is 26.6 per cent.

Pituitary tumors do not seem to contribute to the development of diabetic retinopathy. Whatever the pituitary hormonal influence might be in promoting the development of diabetes, these same diabetogenic factors do not seemingly contribute to the production of diabetic retinopathy.

This rarity of diabetic retinopathy in pituitary tumor patients who develop diabetes mellitus should be considered before pituitary ablation is considered for the removal of diabetogenic factors of the pituitary in a patient with diabetic retinopathy. W.R.K.

Seltzer, Holbrook S.; and Smith, Walter L. (Dept. of Internal Medicine, Univ. of Texas Southwestern Med. Sch., Veterans Administration Hosp., Dallas, Tex.): "PLASMA INSULIN ACTIVITY" IN HUMAN DIABETES DURING HYPOGLYCEMIC RESPONSE TO TOLBUTAMIDE AND INDOLE-3-ACETIC ACID. Proc. Soc. Exper. Biol. & Med. 100:171-74, January 1959.

These authors measured the hypoglycemic responses of normal and diabetic subjects to tolbutamide and indole-3-acetic acid and found that the hypoglycemic responses were similar qualitatively and quantitatively. They were able to confirm the previous observations of Vallance-Owen that normal individuals and mild elderly diabetics demonstrated significant plasma insulin-like activity in their fasting plasma specimens, and both groups exhibited sharp increases in plasma insulin-like activity after the injection of glucose. However, plasma insulin-like activity was not detectable in the blood of juvenile diabetics either before or after glucose administration. In measuring the plasma insulin-like activity in response to the administration of tolbutamide or indole-3-acetic acid, it was found that there was no increase in plasma insulin-like activity in the peripheral blood. These findings are interpreted as possible additional evidence that both tolbutamide and the insulinase inhibitor, indole-3-acetic acid, act by diminishing hepatic glycogenolysis rather than by increasing insulin activity. G.J.H.

Skillern, Penn G.; and Lockhart, George, III (Dept. of Endocrinology & Ophthalmology, Cleveland Clinic Foundation & Frank E. Bunts Educational Inst., Cleveland, Ohio): OPTIC NEURITIS AND UNCONTROLLED DIABETES MELLITUS IN FOURTEEN PATIENTS. Ann. Int. Med. 51:468-75, September 1959.

This is a report on fourteen patients with optic neuritis occurring as a complication of diabetes among several thousand adult diabetic patients. The onset was gradual. The disorder was progressive and bilateral, with objective finding of papillitis or optic atrophy. There were central scotomata or contractions of peripheral vision.

The diabetes was usually poorly controlled, and either undiagnosed or of only relatively short (three months to three years) duration when the condition was first observed ophthalmologically. These patients did not have glaucoma, and only three used tobacco.

The vision improved in only three patients, but did not

progress in the remainder (with one exception) after the diabetes was brought under control. S.B.B.

Sokal, Joseph E.; and Gerszi, Kornell E. (Roswell Park Memorial Inst., Buffalo, N.Y.): HUMAN LIVER GLYCOGEN LEVELS. J. Lab. & Clin. Med. 53:876-81, June 1959.

This report adds thirty-seven determinations of human liver glycogen obtained by biopsy to the literature and summarizes some of the published data from similar studies. A tentative normal range is suggested. An additional case of excessive glycogen storage in diabetes is reported. The median value for liver glycogen in the combined series is 2.16 per cent, and the mean is 2.35 per cent. The upper limit of the normal range, under these conditions of moderate fasting, appears to be about 6 per cent.

There was no correlation between liver glycogen levels and age or diagnosis. No changes in carbohydrate metabolism specific for the age groups or diagnoses represented by these patients have been established.

The liver glycogen levels in six jaundiced patients without severe hepato-cellular damage or evidence of disturbed carbohydrate metabolism, did not differ from those in the remainder of the series.

Although most patients with diabetes have low to normal levels of liver glycogen, like depancreatized animals, an occasional patient has an unusually high level. These patients may represent a special category of clinical diabetes and may be resistant to glucagon. Excessive glycogen storage in one diabetic patient was demonstrable even in the postmortem specimen.

Liver glycogen values in the hepatic form of glycogen storage diseases may reach 12 to 16 per cent. Such values are outside the normal human range, even after high carbohydrate feeding. However, values in the range of 6 to 10 per cent are frequently found. These are above the fasting range indicated by the data reviewed in this paper, but within the normal range following glucose feeding. Lower values have been reported in well-documented cases of glycogen storage disease. Thus, there is considerable overlap between glycogen levels in this disease and the normal range. The diagnosis of hepatic glycogen storage disease should, therefore, be based principally on the characteristic metabolic and biochemical defects, rather than on the liver glycogen concentration. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: I. DESCRIPTION OF METHODS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:99-114, 1958.

A method for simultaneous determination of activity of phosphorylase in rat liver homogenates and determination of the rate of inactivation of phosphorylase in the same homogenate has been described. Problems concerning the method and its application are discussed. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: II. THE ACTIVITY OF LIVER PHOSPHORYLASE IN NORMAL, NONFASTED MALE AND FEMALE RATS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:115-20, 1958.

Male and female nonfasted rats have been examined with respect to activity of liver phosphorylase and rate of inactivation of phosphorylase. The group of female rats showed definitely lower levels of activity of liver phosphorylase as compared with the group of male rats. No difference in the rates of inactivation was demonstrated. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: III. THE ACTIVITY OF LIVER PHOSPHORYLASE IN ADRENALECTOMIZED, NONFASTED RATS AND IN ADRENODEMEDULLATED, NONFASTED RATS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:121-30, 1958.

A group of nonfasted, adrenalectomized rats was examined in regard to levels of active liver phosphorylase. At the same time the rates of inactivation of phosphorylase in homogenates were determined. It was shown that the adrenalectomized rats had levels of activity of phosphorylase in liver which were 75 per cent of the values found in normal, nonfasted animals. The rates of inactivation of phosphorylase in the homogenates were also lower. Also a group of adrenodemedullated animals was examined in the same respects. This group exhibited no differences from a normal group. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: IV. THE INFLUENCE OF STARVATION ON THE ACTIVITY OF LIVER PHOSPHORYLASE IN NORMAL, ADRENALECTOMIZED, AND ADRENODEMEDULLATED RATS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:131-42, 1958.

The activity of liver phosphorylase has been determined in normal rats fasted for eighteen to twenty hours, normal rats fasted for forty-eight hours, adrenalectomized rats fasted for eighteen to twenty hours, and adrenodemedullated rats fasted for eighteen to twenty hours. Normal and adrenodemedullated rats fasted for eighteen to twenty hours showed but little reduction in the activity of liver phosphorylase. The mean value was found to be about 75 per cent of the value for fed animals. Normal rats fasted for forty-eight hours and adrenalectomized rats fasted for eighteen to twenty hours showed values of about 50 per cent of the activity found for fed animals. The rate of inactivation of phosphorylase in the homogenates was reduced in all groups of animals. The reduction was of the same order of magnitude as the decreases in activity of phosphorylase. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: V. THE INFLUENCE OF GLUCOSE LOAD ON THE ACTIVITY OF LIVER PHOSPHORYLASE IN NORMAL AND ADRENALECTOMIZED RATS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:143-61, 1958.

The activity of liver phosphorylase and the rate of inactivation of phosphorylase have been determined in groups of rats loaded with glucose. Normal, nonfasted rats tended to show a decrease in the activity of phosphorylase and an increase in the rate of inactivation of phosphorylase after a glucose load. However, the demonstrated differences were insignificant. Normal, fasted rats and adrenalectomized, nonfasted rats showed a decrease in the activity of liver phosphorylase. A significant increase in the rate of inactivation of phosphorylase was noted in the group of normal, fasted rats only. The results are

discussed, and it is suggested that the altered activity of liver phosphorylase might be mediated via changes in the intracellular electrolytes resulting in an augmented rate of inactivation of phosphorylase. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: VI. THE INFLUENCE OF EPINEPHRINE AND GLUCAGON ON THE ACTIVITY OF LIVER PHOSPHORYLASE. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:162-77, 1958.

Adrenalectomized, nonfasted rats loaded with glucose and simultaneously injected with epinephrine or glucagon were examined with respect to activity of phosphorylase in the liver and rate of inactivation of phosphorylase in the homogenate. Activity of phosphorylase in the liver was higher in the groups examined as compared with control groups treated with glucose alone. The rate of inactivation of phosphorylase was not influenced by the simultaneous treatment with epinephrine or glucagon. Adrenalectomized, nonfasted rats treated with epinephrine alone tended to show an increase in the activity of liver phosphorylase as compared with an untreated group. The difference was, however, not significant. No change was found in the rate of inactivation of phosphorylase.

Adrenalectomized rats, fasted twenty hours, and normal rats, fasted forty-eight hours, treated with glucagon did not show any increase in the activity of liver phosphorylase as compared with untreated control groups. The rate of inactivation of phosphorylase dropped as a result of the treatment with glucagon.

A group of normal, nonfasted rats treated with epinephrine, did not show changes in either activity of liver phosphorylase or in rate of inactivation of phosphorylase as compared with an untreated group. W.R.K.

Sørensen, N. Schwartz (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): STUDIES ON LIVER PHOSPHORYLASE: VII. THE ACTIVITY OF LIVER PHOSPHORYLASE IN RATS TREATED WITH INSULIN AND IN DIABETIC RATS. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:178-85, 1958.

The activity of phosphorylase in the liver of nonfasted, normal rats and adrenalectomized rats was determined thirty minutes after the injection of insulin. It was found that the treatment with insulin did not alter the activity of phosphorylase. Neither did the rate of inactivation of phosphorylase in the homogenate change after the treatment with insulin.

The activity of liver phosphorylase was also determined in a group of nonfasted, alloxan diabetic rats. The activity tended to decrease. The rate of inactivation of phosphorylase in the homogenate was decreased. W.R.K.

Spirtos, B. N.; and Halmi, N. S. (Dept. of Anatomy, State Univ. of Iowa, Iowa City, Ia.): INCREASED INSULIN SENSITIVITY IN RATS WITH HYPOTHALAMIC LESIONS. Endocrinology 65: 669-78, October 1959.

Electrolytic hypothalamic lesions in rats resulted in increased insulin sensitivity. Administration of somatotrophin improved insulin tolerance. A large proportion of the lesion-bearing rats showed regression of pituitary acidophils.

Some animals showed testicular atrophy with accompanying pituitary gonadotrophic cell atrophy. Adrenal atrophy was infrequent. Thyroids and pituitary thyrotrophic cells generally were normal. Charting of the hypothalamic lesions showed no area common to all lesions producing insulin sensitivity.

It is suggested that decreased secretion of somatotrophin resulted in increased insulin sensitivity. H.L.W.

Sprague, Randall G. (Mayo Clinic, Rochester, Minn.): PHYSIOLOGIC PRINCIPLES IN THE TREATMENT OF DIABETIC ACIDOSIS. J. Michigan M. Soc. 58:1653-61, October 1959.

As a consequence of educational efforts on the part of individual physicians, institutions, and the American Diabetes Association, there is probably less diabetic acidosis today than formerly. Nevertheless, there remain ample possibilities for the occurrence of this serious complication of diabetes, and the physician may be confronted with the problem at any time. Its physiologic and therapeutic complexities are so great as to tax the ingenuity and knowledge of any physician called upon to deal with it and strain the resources of whatever institution houses the patient.

Inasmuch as diabetic acidosis in its inception is a state of insulin deficiency, and the patient, in effect, is dying of uncompensated diabetes, insulin must be provided in effective amounts. The most important basic principle of treatment is to give an amount early in the course of treatment which will produce a maximal physiologic effect. A review of failures in the treatment of diabetic acidosis usually will reveal a group of cases in which the major fault clearly was an inadequate amount of insulin.

Conventional treatment with insulin, water and sodium chloride, with or without glucose, may induce important disturbances of electrolytes in addition to those which were present before therapy was begun. In a significant proportion of fatal cases, after apparently good initial progress, death occurs about eight to sixteen hours after initiation of therapy, at a time when ketogenesis has been arrested, hyperglycemia corrected and hydration restored. Frequently, necropsy in such cases does not disclose an anatomic basis for death, and it is difficult to escape the conclusion that the treatment itself may have contributed in some manner to the fatal outcome.

In the early hours of treatment, the most important aspect of electrolyte therapy is correction of deficits of sodium and chloride.

To avoid hyperchloremia, solutions may be employed which contain approximately 100 mEq. or less of chloride and 150 mEq. or less of sodium per liter. With the electrolyte solutions for intravenous administration, which are now available, and the supplementary solutions that may be added to them, it is a relatively simple matter to prepare solutions containing both sodium and chloride ion in approximately physiologic amounts.

In the treatment of severe acidosis, administration of potassium is started approximately four to six hours after the initiation of therapy, provided that the output of urine is satisfactory and adequate amounts of insulin have been administered.

In contrast to potassium, the clinical implications of phosphorus deficiency and hypophosphatemia are not clear. Losses of water in severe diabetic acidosis may be extreme, sometimes amounting to 10 per cent or more of body weight. Replacement of fluids and other treatment may fail to prevent or correct circulatory collapse.

Failure of the hematocrit to fall 5 to 10 per cent in the first few hours of treatment with adequate amounts of intravenously administered fluid and electrolytes indicates that the desired dilution of blood is not occurring because too much of the administered fluid is leaving the circulation. Under these circumstances, or in the presence of frank shock, transfusions of plasma, whole blood or colloid solutions such as dextran may help to correct a potentially serious situation. Levofed may occasionally be lifesaving.

There will continue to be a small number of irretrievably ill patients who will die in diabetic acidosis, or soon after its correction, in spite of the most expert treatment. However, if present-day knowledge of treatment is skillfully applied, this group should be made up, for the most part, of patients who arrive at the hospital in irreversible shock or with severe complicating illness. W.R.K.

Stein, Olga; and Gross, Jack (Hebrew Univ., Hadassah Med. Sch., Jerusalem, Israel): THE LOCALIZATION AND METABOLISM OF I^{131} INSULIN IN THE MUSCLE AND SOME OTHER TISSUES OF THE RAT. Endocrinology 65:707-16, October 1959.

I^{131}-labeled insulin injected into rats localized to a significant degree in muscle and kidney. Homogenation and differential centrifugation showed a concentration of labeled insulin in the soluble protein fraction of thigh muscle. Autoradiograph demonstrated even distribution of the radioactivity throughout the cell.

In vitro incubation of I^{131} insulin with diaphragm showed concentration of the radioactivity in the fascia covering the muscle.

The intracellular localization of insulin in thigh muscle suggests that insulin does not facilitate glucose entry by its action at the cell surface but rather that it inhibits within the cell a process which otherwise deters the entry of glucose. H.L.W.

Steiner, Donald F.; and Williams, Robert H. (Dept. of Med., Univ. of Washington School of Med., Seattle, Wash.): SOME OBSERVATIONS CONCERNING HEPATIC GLUCOSE 6-PHOSPHATE CONTENT IN NORMAL AND DIABETIC RATS. J. Biol. Chem. 234:1342-46, June 1959.

The concentration of glucose 6-phosphate in the rat liver was measured by the reduction of TPN in the presence of a glucose-6-P dehydrogenase preparation. Its concentration was increased by feeding the animals, also by giving them glucagon, glucose or fructose. Producing diabetes by means of alloxan caused a fall in enzyme content despite feeding. Insulin administration failed to alter the hepatic glucose 6-phosphate level in fasted normal or in diabetic animals. It is possible that changes in enzyme concentration may play a role in regulation of glucose utilization by the rat liver through the hexose monophosphate shunt pathway. A.R.C., Jr.

Sugar, Samuel J. N.; Thomas, Lawrence J.; Eugenio, Teodora M.; and Tatlier, Serkis (Med. Dept., Prince George's Gen. Hosp., Cheverly, Md., and Diabetic Clin., George Washington Univ. Div., District of Columbia Gen. Hosp., Washington, D.C.): PHENFORMIN (DBI) IN THE MANAGEMENT OF DIABETES MELLITUS. M. Ann. District of Columbia 28:426-31, 476, August 1959.

It has been suggested that DBI acts in the diabetic patient by increasing anaerobic glycolysis and decreasing gluconeogenesis from protein. These actions are not confirmed by clinical observation. Of forty-seven patients studied, DBI was effective in a significant proportion of stable and unstable mature diabetics. Unstable diabetics of any age should be managed with insulin before trial with DBI. W.R.K.

Vannas, S.; Hernberg, C. A.; and Björkesten, G. (Helsinki, Finland): HYPOPHYSECTOMY AS A THERAPEUTICAL METHOD FOR PROLIFERATIVE DIABETIC RETINOPATHY. A.M.A. Arch. Ophth. 62:370-80, September 1959.

Most authors seem to hold that impairment of vision generally ends after hypophysectomy and the process becomes less active and that retinopathy hardly progresses at all. Kinsell, in whose material three of nine patients survived for over one year, came to a more negative conclusion of the effect of hypophysectomy. The authors' observation was that the changes of the venules and capillaries and the newly formed vessels seemed to hold a key position even after hypophysectomy. First, new hemorrhages were possible in this particular area, even after hypophysectomy. Secondly, the changes on the venous side might regress, even disappear, after hypophysectomy. It would be important to know how often and how completely the positive changes mentioned, namely, narrowing of venules and the disappearance of the dilated capillaries and the micro- and macroaneurysms and the newly formed vessels, really occur. Certain positive changes notwithstanding, it must be emphasized that the risk involved is considerable and constant attention must be paid in postoperative care both to the hormone-electrolyte balance and to the danger of infections. Although the patients of this type have an extremely gloomy prognosis, it is not yet possible to make a final evaluation of hypophysectomy as a clinical therapeutic method against proliferative diabetic retinopathy. W.R.K.

Volk, Bruno W.; and Lazarus, Sydney S. (Dept. of Pathol., Albert Einstein Coll. of Med., Bronx, N.Y.): EFFECT OF ADRENALIN ON BLOOD GLUCOSE AND PANCREATIC MORPHOLOGY. Endocrinology 65:586-93, October 1959.

Both glucagon and adrenalin cause hepatic glycogenolysis. Cortisone increases hepatic glycogen content. A previous study has shown that pretreatment of rabbits with a subdiabetogenic dose of cortisone not only augments the hyperglycemic action of glucagon but produces a sustained hyperglycemia.

Similar pretreatment of rabbits with cortisone results in an augmentation of adrenalin action but of a much more transient nature. It is not apparent why sustained hyperglycemia does not result.

The pancreases of animals long-term treated with cortisone plus adrenalin showed hyperplastic islets, islet proliferation from duct epithelium, beta cell degranulation without beta cell destruction, and glycogen deposition in ductular epithelium. H.L.W.

Wakil, Salih J.; and Ganguly, J. (Inst. for Enzyme Res., Univ. of Wisconsin, Madison, Wisc.): ON THE MECHANISM OF FATTY ACID SYNTHESIS. J. Am. Chem. Soc. 81:2597-98, May 20, 1959.

The first step in fatty acid synthesis is the carboxylation of acetyl Co A to malonyl Co A catalyzed by a biotin-containing enzyme fraction in the presence of ATP. Malonyl Co A is converted to palmitate in the presence of TPNH. A significant amount of C^{14} acetyl Co A, C^{14} butyryl Co A and C^{14} octanoyl Co A can also be converted to palmitate in the presence of unlabeled malonyl Co A. Acetaldehyde was not formed by the enzymatic reduction of acetyl Co A by TPNH.

The oxidation of TPNH in the system used requires the combined presence of malonyl Co A and some unsubstituted fatty acyl Co A. None of the intermediates of β oxidation can replace these fatty acyl Co A esters. These observations suggest that there are distinct enzymatic pathways of fatty acid synthesis and of fatty acid oxidation. J.A.

Weinstein, Albert (Nashville, Tenn.): TAILORING INSULIN, INSULIN-SUBSTITUTE TABLETS, AND DIET. J. Arkansas M. Soc. 56:179-84, October 1959.

The management of a diabetic in the last decade has been simplified and the use of insulin can be even more simplified. The author warns against oversimplification in the treatment of this disorder. This, too, can lead to sins of omission and commission. We will always have the problems of tailoring insulin, diet, and, in general, the specific care for each patient, rather than having a general plan that provides for all our patients. W.R.K.

Weitze, Marie (Steno Memorial Hosp. and Nordisk Insulinlaboratorium, Copenhagen, Denmark): FACTORS INFLUENCING THE SENSITIVITY OF MICE TO INSULIN. Rep. Steno Memorial Hosp. & Nordisk Insulinlaboratorium 7:186-98, 1958.

Female mice are more sensitive to insulin than male mice. The sensitivity of mice to insulin depends on body weight. With increasing body weight, sensitivity increases. In mice with a body weight of more than 28 gm. sensitivity increases when body weight is augmented. Sensitivity increases during the day until about 2 a.m., then suddenly decreases, remaining low during the remainder of the night and early morning. Sunshine influences sensitivity, an increasing amount of sunshine making the mice more resistant to insulin. By keeping the mice in darkness for a longer time than that of the average night the influence of sunshine is reduced. W.R.K.

Whitehouse, Fred W.; and Bryan, Henry G. (Div. of Metabolic Disease, Henry Ford Hosp., Detroit, Mich.): GLUCAGON FOR TREATMENT OF INSULIN HYPOGLYCEMIA: ITS USE IN THE PATIENT WITH DIABETES. Am. Pract. & Digest Treat. 10:1326-30, August 1959.

The authors have explored the parenteral use of a purified form of glucagon in the treatment of insulin hypoglycemia in human diabetic patients. Glucagon was given subcutaneously in doses of 1 to 2 mg. An average rise of blood sugar of 53 mg. per 100 cc. occurred twenty minutes after injection in a group of ten patients, with a range of 3 to 105 mg. per 100 cc. blood. For severer degrees of hypoglycemia, a 2 mg. dose was required. No commercial preparation is available. S.B.B.

Wilkerson, Hugh L. C. (Diabetes Field Res. and Training Unit, U.S. Dept. of Health, Education, and Welfare, Brighton, Mass.): MATERNAL PREDIABETES AND OUTCOME OF PREGNANCY: A PRELIMINARY REPORT. Am. J. Pub. Health 49: 1032-40, August 1959.

For purposes of this study the status of carbohydrate metabolism in pregnancy is determined by giving a standard three-hour, 100-gm. glucose tolerance test to all pregnant women who meet one or more of the following screening criteria:

1. A venous blood sugar (true glucose) of 130 mg./100 ml. or more, one hour after taking 50 gm. of glucose by mouth.
2. A history of diabetes in the family.
3. A history of having borne a baby weighing nine pounds or more.
4. A history of any of the following in two or more pregnancies: (a) fetal death, (b) neonatal death, (c) congenital anomaly, (d) prematurity, and (e) toxemia (excessive weight gain, hypertension, albuminuria).

All women with an abnormal GTT in any trimester who have not reached the thirty-seventh week of pregnancy are selected for the study. Every second woman with an abnormal GTT is selected for insulin therapy for the remainder of her pregnancy. No insulin is given after delivery, except when indicated, because of evidence of clinical diabetes existing postpartum. Those women with abnormal glucose tolerance tests for whom insulin is not prescribed are observed as controls. In addition, a random sample of women regardless of screening results but confirmed as being normal by glucose tolerance tests repeated in each trimester are selected for long-term follow-up. These have been designated "negative controls."

Through June 30, 1958, of the total number of 14,988 pregnant women screened, 6,332 screened positive by one or more criteria. Of 5,523 women who had had at least one glucose tolerance test, 478 had at least one positive test, representing 8.7 per cent of those who received the tolerance test, or 3.2 per cent of the total number of women screened.

Of 191 women who had had a normal glucose tolerance test in the first trimester, three or 1.6 per cent were abnormal on repeat test in the second trimester. Of 1,781 women normal in the first and/or second trimester, 147 or 8.3 per cent had become abnormal in the third trimester. At present there are 208 in the "insulin treated" group and 212 in the "positive control" group. In addition, 209 women with normal glucose tolerance tests have been randomly selected as "negative controls."

The "positive controls," in contrast to the "insulin treated" group, received no special treatment for their abnormal carbohydrate metabolism. All groups were given the best possible prenatal care and were treated in the same manner during the period of confinement and delivery, except for purely obstetrical or medical indications outside of the abnormal carbohydrate condition.

The "positive control" group, therefore, have a significantly larger number of babies weighing nine pounds or more than the mothers in the "insulin treated" group; the congenital anomalies and neonatal deaths are more numerous in the "positive control" group, but the difference is not significant at the level of $P = 0.95$. There is no significant difference between the number of fetal deaths in the two groups.

In all respects the outcome of pregnancy in the "insulin treated" group appears to be the same or very similar to that in the "negative control" group.

The average age and average degree of obesity or overweight in the "positive control" and the "insulin treated" groups are about the same. Yet, with insulin therapy, differences appear in the outcome of pregnancy in three respects, only one of which, at this time, is considered to be statistically significant. W.R.K.

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20th ANNUAL MEETING
JUNE 11-12, 1960

The Association's Twentieth Annual Meeting will be held in Miami Beach, Florida, June 11-12, 1960, at the Deauville Hotel, just prior to the annual session of the American Medical Association. Five, instead of the customary three, Scientific Sessions have been scheduled, and approximately forty papers will be presented. The first Session will be held Saturday morning, June 11; the second, Saturday afternoon concurrently with the business meeting of the Assembly of Delegates. (For further details about other meetings for Delegates see the March-April issue of THE AFFILIATE BUILDER.) There will be two concurrent Scientific Sessions, one experimental and the other clinical, on Sunday morning and a final Session Sunday afternoon, June 12. Blair Holcomb, M.D., is Chairman of the Committee on Scientific Programs. Among highlights of the Sessions:

- Priscilla White, M.D., of the Joslin Clinic and the New England Deaconess Hospital, Boston, Massachusetts, will deliver the Banting Memorial Lecture. Her subject will be "Childhood Diabetes—Its Course, and Influence upon the Second and Third Generations."

- Albert E. Renold, M.D., winner of the 1960 Lilly Award, will present a paper tentatively entitled "The Use of Adipose Tissue for the Measurement of Insulin-like Activity: Problems and Progress Report." Dr. Renold is Assistant Professor of Medicine, Harvard Medical School; Director, Baker Clinic Research Laboratory, Boston.

- Irving H. Leopold, M.D., will present a summary of the Symposium on Retinopathy which is being held in Cherry Hills, New Jersey, May 1-2, by the National Institute of Neurological Diseases and Blindness. Dr. Leopold, who will chair the Symposium, is Chairman, Department of Ophthalmology, The Graduate School of Medicine, University of Pennsylvania, Philadelphia.

Members and their wives (or husbands) and friends are invited to attend the Annual Banquet and Social Hour Saturday evening, June 11. A reservation form for the Banquet will be mailed a few months prior to the meeting.

A special hotel reservation card was sent in November to all Association members. Those who have not yet made reservations are urged to do so immediately by filling out the card and sending it directly to the Deauville Hotel.

Members who plan to attend the ADA Annual Meeting and wish to stay over at the same hotel for the annual meeting of the American Medical Association on June 13-17, should inform the Deauville Hotel that they would like to continue their ADA reservation for the AMA sessions.

DIABETES will publish a list of papers to be given at the Scientific Sessions; and the program itself, including abstracts of all papers presented or read by title, will be sent to all members without charge before the meeting.

Members and nonmembers may secure additional copies of the final program at a cost of $1.00 each by requesting them from the American Diabetes Association, 1 East 45th Street, New York 17, N.Y. The program also will be available at the Registration Desk in Miami Beach for those who wish to purchase one at the time of the Meeting.

NEW EDITOR AND CHAIRMAN, EDITORIAL BOARD, NAMED

Frank N. Allan, M.D., Boston, as Chairman of the Committee on Scientific Publications, announces the appointment of Irving Graef, M.D., New York, as Editor of DIABETES: *The Journal of the American Diabetes Association,* and Francis D. W. Lukens, M.D., Philadelphia, as Chairman of the Editorial Board. Dr. Graef was Associate Editor from Jan. 1, 1956, until his recent appointment as Editor. Dr. Lukens has been a member of the Editorial Board from the inception of the Journal in January 1952, and is President of the American Diabetes Association.

9th POSTGRADUATE COURSE

The American Diabetes Association will hold its Ninth Postgraduate Course in Diabetes and Basic Metabolic Problems in New Orleans, Jan. 18-20, 1961. Further details will be published in the Journal at a later date.

ADA AMENDS BYLAWS

The Council of the American Diabetes Association on Jan. 23-24, 1960, adopted the following amendments to the Bylaws: *Amendment of Article I "Membership," Section 1 "Classes of Members," Paragraph 4 "Corporate Members":*

4. *Corporate Members.* Medical, welfare, civic, educational, scientific, business or other organizations may be elected to Corporate Membership, Contributing Corporate Membership or Sustaining Corporate Membership. These categories shall be determined by the amount of the contribution and the amount of the contribution characterizing each category shall be fixed by the Council from time to time.

Amendment of Article XV "Amendments to Bylaws":

These Bylaws may be amended by the following procedure:

First, amendments may be proposed by the joint action of any three or more Councilors at any regular or special meeting of the Council.

Second, the Council shall, by a majority vote of those present accept or reject, in principle, any such amendment.

Third, any proposal so accepted shall be referred to the Committee on Constitution and Bylaws which shall be responsible for seeing that the proposed amendment does not conflict with other provisions of the Constitution and Bylaws and for casting them in appropriate language and shall transmit them to the Secretary at least sixty days before the next meeting of the Council.

Fourth, the Secretary shall send a copy of such proposed amendment to each member of the Council at least twenty days before its next meeting.

Fifth, upon the favorable vote of at least two thirds of the members of the Council present at the next meeting such proposed amendment shall be adopted.

ADA RESEARCH FELLOWSHIPS

The Committee on Research and Fellowships of the American Diabetes Association will award at least three Research Fellowships for the academic year July 1, 1961—June 30, 1962. Deadline for applications is Nov. 15, 1960. Requests for application forms and other inquiries should be addressed to Mr. J. Richard Connelly, Executive Director, who will forward the information to the Committee.

1961 LILLY AWARD

The fifth Lilly Award will be given at the Twenty-first Annual Meeting of the American Diabetes Association June 24-25, 1961, in New York City. The following stipulations govern the contest for this annual award, which is supported by Eli Lilly and Company and consists of $1,000 and a medal.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before December 1 of the year preceding the award. The nomination should be accompanied by full information concerning the nominee's personality, training and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to December 1 of the year preceding the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

8th GRADUATE AND MEDICAL STUDENT-INTERN ESSAY CONTEST

Members of the American Diabetes Association and subscribers to DIABETES are asked to encourage medical students, interns, and physicians within two years after their graduation from medical school, and graduate students in the basic sciences to enter the 1959-60 Graduate and Medical Student-Intern Essay Contest.

An award of $250 will be given to the author or authors of the best paper reporting original work, whether laboratory

investigation or clinical observation. One hundred dollars ($100) will be awarded for the best review article or case report.

The papers will be judged on the basis of the value of the material and method of presentation. Any subject relating to diabetes and basic metabolic problems may be selected.

Papers entered in the Contest should not have been previously published. Appropriate manuscripts may be considered for publication in DIABETES: *The Journal of the American Diabetes Association.*

Contestants should submit the original and two copies of their papers. Typewritten and double-spaced, all manuscripts should be mailed by April 1, 1960, to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th Street, New York 17, N.Y.

APPOINT PROGRAM ADVISORY COMMITTEE FOR IDF CONGRESS

Howard F. Root, M.D., Boston, Chairman, Alexander Marble, M.D., Boston, and Franklin B. Peck, Sr., M.D., Indianapolis, comprise the recently named Advisory Committee for the program of the Fourth Congress of the International Diabetes Federation, which will be held July 10-14, 1961, in Geneva, Switzerland. Further information about the Congress will be published in the Journal as soon as it is available.

CHANGE IN COMMITTEE NAMES

"Committee on Oral Hypoglycemic Compounds" is the new name of the Committee formerly known as "Informational Committee on Oral Hypoglycemic Compounds." Also, the name of the "Subcommittee on Standardization of the Committee on Professional Education" has been changed to "Subcommittee on Definition and Classification of the Committee on Professional Education." These changes were effected at the recommendation of the respective Committees at the 1959-60 Interim Council Meeting held Jan. 23-24, 1960, in Los Angeles.

TEACHING AND RESEARCH IN DIABETES STILL AVAILABLE

The proceedings of the first National Conference on Teaching and Research in Diabetes are still available without cost by addressing your request to the American Diabetes Association, Inc., 1 East 45th Street, New York 17, N.Y. Entitled *Teaching and Research in Diabetes,* the proceedings were edited by E. Perry McCullagh, M.D. The Conference Committee included E. Perry McCullagh, M.D., Chairman, Arthur R. Colwell, Sr., M.D., John E. Howard, M.D., Thomas McGavack, M.D., and Robert H. Williams, M.D.

The first National Conference was held in Atlantic City, New Jersey, May 3, 1958, under the sponsorship of the American Diabetes Association and the National Institute of Arthritis and Metabolic Diseases, Public Health Service, U.S. Department of Health, Education, and Welfare.

SUMMER CAMP LIST IN *ADA FORECAST*

Physicians and other interested persons who may wish to help diabetics and their families will be interested to know that a list of "Summer Camps for Diabetic Children" is scheduled for the May-June FORECAST. Sponsorship of the camp will be given, as well as camping dates, rates, ages of children accepted at particular periods, and the name and address of the contact officer. Copies of the May-June issue may be obtained after April 15 at 35¢ each or six for $2.00. Single copies of reprints of the camp list may be secured without charge.

DIABETES WEEK 1960

The week of November 13-19 will be observed as Diabetes Week, following the usual practice of observing official Diabetes Week the week before Thanksgiving. Affiliate Associations and Committees on Diabetes Detection of County and State Medical Societies are urged to note these dates in making plans for Public Education and Detection programs.

NEW MEMBERS

The following were elected as of Feb. 1 and March 1, 1960.

Active

California	
Carlson, E. O.	Ontario
Fanson, Ethel	Pasadena
Holvey, Sherman M.	Los Angeles
Johnson, Robert W.	Pomona
Litman, Neil N.	Los Angeles
Renshaw, R. John F.	Santa Ana
Schoon, Doris V.	Anaheim
Schwartz, Mervyn U.	Fresno
Wile, David E.	San Diego
Kansas	
Donnell, James M.	Wichita
Louisiana	
Tolbert, Louis E., Jr.	New Orleans
Massachusetts	
Amador, Andres	Boston
Ferguson, B. Dan	Boston
Michigan	
Hagele, Marie A.	Sault Ste. Marie
New York	
Birtch, Paul K.	Buffalo
Fernbach, Paul A.	Buffalo
Finger, Louis	New York City
Gibbons, Donald	New York City
Haft, Donald E.	New York City
Taylor, Frederic F.	Watertown
Pennsylvania	
Green, Stanley	Philadelphia
Lewis, Robert E.	Pittsburgh
Winegrad, Albert I.	Philadelphia
Rhode Island	
Tetreault, Albert F.	Providence
Texas	
McMahon, David T., Jr.	San Antonio

Associate Member

Georgia	
Pennington, Alice H.	Milledgeville

NEWS OF AFFILIATE ASSOCIATIONS

The NEW ENGLAND DIABETES ASSOCIATION held a fall clinical meeting at the Joslin Auditorium in Boston on Dec. 1, 1959. Guest speaker was James M. Salter, Ph.D., Toronto, who spoke on glucagon. He was introduced by Louis I. Kramer, M.D., of Providence, Rhode Island, who is president of the Affiliate.

The winter meeting of the New England Diabetes Association was held Feb. 1, 1960, at the Rhode Island Medical Library in Providence. A panel entitled "The Use of Oral Agents in the Treatment of Diabetes Mellitus" was presented with the following participants: Louis I. Kramer, M.D., Chairman, Samuel B. Beaser, M.D., Leo P. Krall, M.D., and Albert E. Renold, M.D.

The NEW YORK DIABETES ASSOCIATION (Clinical Society) held a meeting at the New York Academy of Medicine on Feb. 25, 1960, at which the following papers were presented: "The Vascular Stigmata of Diabetes," by George V. Mann, M.D., Nashville, with discussion opened by Harold Rifkin, M.D.; and "Newer Pharmacological Approaches to the Hypercholesterolemia of Diabetes," by Stanley Bergen, M.D., with discussion opened by Daniel Rudman, M.D.

NEWS NOTES

NATIONAL VITAMIN FOUNDATION INVITES RESEARCH GRANT APPLICATIONS

The National Vitamin Foundation invites applications for grants-in-aid for research on vitamin nutrition and metabolism in the areas of (1) mental health, and (2) skin eruptions related to drug ingestion and allergies. Research projects in these two areas will receive preferential consideration; however, the Foundation also will consider applications for research grants on other aspects of vitamin nutrition and metabolism.

Application forms for grants-in-aid can be obtained from the offices of the Foundation at 149 East 78th Street, New York 21, N. Y. The Foundation takes action on applications twice each year, in the spring and fall. For grants to be effective July 1, applications should be mailed to the Foundation before the preceding March 1; for January grants, applications should be in the possession of the Foundation by September 15.

ADA MEMBERS TO TAKE PART IN POSTGRADUATE COURSES

The following members of the American Diabetes Association will participate in postgraduate courses presented by The American College of Physicians during the spring of 1960:

Robert H. Williams, M.D., will be Director of Postgraduate Course No. 1, "Recent Advances in Pharmacotherapy," which will be presented March 21-25, 1960, at the Health Sciences Auditorium of the University of Washington School of Medicine in Seattle. He also will be moderator of the March 21 morning session and speak on "Oral Antidiabetic Drugs" on March 24. Laurance W. Kinsell, M.D., San Francisco, will be among the guest faculty and will speak on "Lipostatic Agents" and "Treatment of Obesity." Joseph H. Crampton, M.D., and Belding H. Scribner, M.D., will be members of the faculty, the former speaking on "The Therapeutic Approach to Nontoxic Goiter," and the latter acting as moderator of the March 25 afternoon session. Dr. Scribner will speak on "The Role of the Artificial Kidney in the Management of Acute Renal Failure" and participate in a "Panel Discussion on Pyelonephritis."

Harry N. Hoffman, M.D., Rochester, Minnesota, Dwight L. Wilbur, M.D., San Francisco, Salvador Zubiran, M.D., Mexico City, and Grace Goldsmith, M.D., will be officers of instruction for Postgraduate Course No. 2, "Current Concepts in Gastroenterology," which will be held March 28-31, 1960, at the Louisiana State University School of Medicine in New Orleans. Dr. Hoffman will speak on "Current Concepts of Bilirubin Metabolism and Jaundice"; Dr. Wilbur on "Diagnosis and Management of Functional Gastrointestinal Disorders"; and Dr. Zubiran on "Nutritional Aspects of Gastrointestinal Disease." Dr. Goldsmith will present a clinical demonstration entitled "Nutrition."

Postgraduate Course No. 4, entitled "Early Detection and Prevention of Disease," will be presented May 9-13, 1960, at the University of Pennsylvania School of Medicine in Philadelphia. Garfield G. Duncan, M.D., and Leo J. Wade, M.D., New York, will be officers of instruction. Dr. Duncan will speak on "A Critical Evaluation of the Possibilities and Technics for the Early Detection or Prevention of Diabetes Mellitus and Its Complications," and Dr. Wade on "Experience with the Periodic Health Examination in an Occupational Medical Program."

Edgar S. Gordon, M.D., Madison, Wisconsin, will be among the guest faculty for Postgraduate Course No. 7, "Internal Medicine," which will be presented June 20-24, 1960, at the Indiana University School of Medicine in Indianapolis. James Ashmore, Ph.D., Glenn W. Irwin, M.D., William R. Kirtley, M.D., James O. Ritchey, M.D., and Charles E. Test, M.D., will be members of the faculty. Dr. Ashmore will speak on "Endocrine Regulation of Carbohydrate Metabolism." Dr. Irwin will present "Management of Nontoxic Goiter" and "Problems in the Diagnosis and Treatment of Cushing's Syndrome." He also will participate in a "Panel Discussion on Treatment of Hyperthyroidism." Dr. Kirtley will speak on "Oral Hypoglycemic Drugs"; Dr. Ritchey on "Xanthomatosis"; and Dr. Test on "Some Problems in Management of Labile Diabetes."

ADA IDENTIFICATION CARD

An identification card for diabetics, issued by the American Diabetes Association, is available. This card was developed by the Committee on Information for Diabetics, bears the official seal of the Association, and will fit the average pocket or purse wallet. The price is $.10 each in quantities of one through nine and $.05 each in quantities of ten or more, both prices including handling and shipping.

ADA MEMBERS PARTICIPATE IN ENDOCRINOLOGY COURSE

The following members of the American Diabetes Association will take part in a continuation course in "Endocrinology for

WHAT YOU CAN DO TOMORROW

Every member of the American Diabetes Association, by joining and by participating in the Association's work, has expressed a strong interest in the accomplishment of the Association's basic objectives. Some members, having considered the necessity for strengthening the Association's program, and having desired to extend their support into the future, have inquired about procedures for remembering the Association through personal legacies.

Each year, as additional demands are made on the Association's program, it is more difficult to be certain that annual income will provide for the necessary minimum expansion in coverage. As a consequence these legacies, and the kind of interest that they imply, will be of more and more importance in insuring the continued effectiveness of the Association's work.

If, in planning the details of your estate with your attorney, you should wish to consider a general bequest to the American Diabetes Association, he may find it helpful to have available the following form:

I hereby give and bequeath to the American Diabetes Association, Inc., a corporation organized under the laws of the State of Ohio, having its principal office at 1 East 45th Street, New York 17, N.Y., the sum of ..... dollars.

Bequests to the Association are exempt from estate taxes, and other possible tax advantages should also be discussed with your attorney, as should methods for providing for gifts of real property, cash and securities. Any questions may be referred to the American Diabetes Association, 1 East 45th Street, New York 17, N.Y.

Physicians," which will be held March 28-April 1, 1960, at the University of Minnesota Center for Continuation Study in Minneapolis.

William W. Engstrom, M.D., Milwaukee, and Alexander Marble, M.D., Boston, will be guest speakers.

March 28: In the morning session on "The Thyroid," Edmund B. Flink, M.D., will be Chairman. Dr. Engstrom will speak on "Nature and Action of Thyroid Hormone: Thyroid Hormone Transport"; and William M. McConahey, M.D., on "Thyroiditis." In the afternoon, F. Raymond Keating, Jr., M.D., will present "Myxedema" and "Treatment of Hyperthyroidism." Drs. Engstrom and Keating will participate in a "Panel Discussion on Cases of Thyroid Disorders."

March 29: B. J. Kennedy, M.D., will be Chairman of the morning session on "The Male and Female Gonads," and Wyman E. Jacobson, M.D., will be Chairman of the afternoon session. Dr. Kennedy will speak on "The Hirsute Woman," and will participate in a "Panel Discussion on Ovarian Dysfunction." Dr. Jacobson will speak on "Male Hypogonadism."

March 30: Dr. Keating will speak on "Tumors of the Adrenal Medulla" and Robert M. Salassa, M.D., on "Aldosteronism," as part of the morning session on "The Adrenals: Adrenal Cortical Treatment." In the afternoon, when Frederick C. Goetz, M.D., will be Chairman, Dr. Salassa will speak on "Cushing's Syndrome," and will participate in a "Panel Discussion on Borderlands of Adrenal Dysfunction," with Dr. Flink as Moderator.

March 31: In the morning session, Dr. Flink will speak on "Osteomalacia, Osteoporosis and Other Bone Diseases," during a session on "Calcium Metabolism." In the afternoon, Raymond V. Randall, M.D., will speak on "True Hypopituitarism," as part of the session on "The Pituitary Gland," of which Dr. Goetz is Chairman. Dr. Goetz also will moderate a panel discussion in which Dr. Randall will take part.

April 1: The day will be devoted to "Diabetes Mellitus," with Dr. Flink as Chairman of the morning session. The program will include: Arnold Lazarow, M.D., Ph.D., "The Nature of Diabetes"; Dr. Marble, "Present-day Insulin Preparations and What They Can Accomplish"; Laurentius O. Underdahl, M.D., "What Is the Optimum Diet in Diabetes?"; Dr. Marble, "The Present Place of Oral Substitutes for Insulin"; Dr. Goetz, "Special Problems of the Diabetic Patient with Kidney Disease." Dr. Goetz will be Chairman of the afternoon session, when the following papers will be presented: "Vascular Disease in the Diabetic Patient as Seen by the Surgeon," by Victor A. Gilbertsen, M.D.; "Eye Complications of Diabetes," by John E. Harris, M.D.; "Diabetic Acidosis," by Dr. Flink; "Diabetes in Childhood and Adolescence," by Dr. Underdahl; "Panel Discussion on Young Adults with Diabetes," with Dr. Goetz as Moderator, and Drs. Flink, Marble and Underdahl as participants.

PERSONAL

ROBERT F. LOEB, M.D., New York, has been named by President Eisenhower to the President's Science Advisory Committee for a three-year term.

SYDNEY S. LAZARUS, M.D., M.Sc. (MED.), and BRUNO W. VOLK, M.D., Brooklyn, will present a paper entitled "Morphology and Pathogenesis of Maturity Onset Diabetes" at the session of the New York Pathological Society in affiliation with The New York Academy of Medicine, which will be held March 24 at 8.30 p.m.

MAXWELL SPRING, M.D., New York, has been elected President of the Bronx Chapter of the New York State Society of Internal Medicine.

NECROLOGY

DAVID ADLERSBERG, New York, New York, born July 23, 1897.

JEROME J. GREENWALD, Malverne, New York, born April 27, 1913.

DAVID M. KURSCHNER, Bronx, New York, born November 4, 1903.

WALTER G. REDDICK, Dallas, Texas, born January 24, 1899.

SELMA WEISS, Newark, New Jersey, born August 28, 1894.

JAMES T. WORTHAM, Little Rock, Arkansas, born September 10, 1924.